IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: WALLACH et al

Appln. No.: 08/485,129

Filed: June 7, 1995

For: ISOLATED DNA ENCODING TUMOR NECROSIS FACTOR BINDING PROTEIN II, AND VECTORS, HOSTS AND PROCESSES USING SUCH DNA



Art Unit: 1644

Examiner: R. Schwadron

Washington, D.C.

March 23, 2000

Atty.Docket: WALLACH=5B



## BRIEF ON APPEAL

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Submitted herewith is applicant's Brief on Appeal in triplicate.

The present appeal is taken from the action of the examiner in finally rejecting claims 11-13, 35-38, 43, 44, 46-49 and 51. The full text of claims 11-13, 35-38, 43, 44, 46-49 and 51 under appeal appears in Appendix A attached hereto.

## REAL PARTY IN INTEREST

The present application is owned by Yeda Research and Development Co. Ltd., which is the research and development arm of the Weizmann Institute of Science in Rehovot, Israel. The exclusive licensee of the present invention is Inter-Lab Limited,

an Israeli company of Ness-Ziona, Israel. Inter-Lab Limited is a subsidiary of InterPharm Laboratories Limited, an Israeli company of Ness-Ziona, Israel, which is a subsidiary of Ares Serono N.V., whose parent company, Ares Serono S.A., is a holding company under which there are many subsidiaries worldwide.

## RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

The present application is a divisional of parent application 07/930,443, filed August 19, 1992. All of the claims in the present case are drawn to invention(s) deleted from the parent application in light of a restriction requirement. The claims remaining in said parent application drawn to the TBP-II protein are now involved in an interference proceeding with the claims of U.S. patent 5,344,915. This is pending interference no. 103,625. While it is not believed that this interference will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal, it is nevertheless being brought to the Board's attention as it is related in the sense discussed above, and the examiner has required that the reference to this interference be made in the present section of the appeal.

## STATUS OF CLAIMS

Claims 11-14, 35-39 and 43-51 presently appear in this case. Claims 11-13, 35-38, 43, 44, 46-49 and 51 are under final rejection. Claims 1-10, 15-34 and 40-42 have been cancelled. Claims 14, 39, 45 and 50 have been withdrawn from consideration, but it is understood that in the event that the claims on appeal are found allowable, these withdrawn claims will be treated as per MPEP §821.04.

## STATUS OF AMENDMENTS

A final rejection was issued in this case on July 2, 1997. On November 3, 1997, an amendment after final was filed. By Advisory Action of December 2, 1997, the proposed amendment were entered. On March 31, 1998, another amendment after final rejection was filed, and on April 3, 1998, a further supplemental amendment after final rejection was filed. However, this latter supplemental amendment contained a request under 37 C.F.R. §1.129(a) that the finality of the official action of July 2, 1997, be withdrawn. By the official action of July 6, 1998, the examiner withdrew the finality of the previous office action and confirmed that all of applicants' amendments after final rejection of November 6, 1997, March 31, 1998, and April 3, 1998, had been entered.

On February 26, 1999, another final rejection was issued by the examiner. Subsequent to the final rejection of February 26, 1999, applicant filed an amendment on May 25, 1999, and a

supplemental communication submitting three certified Israel priority documents on July 8, 1999. By Advisory Action of August 20, 1999, the examiner indicated that upon filing of an appeal, the proposed amendment would be entered. The examiner also entered and considered the supplemental communication and the Israeli priority documents.

## SUMMARY OF THE INVENTION

The present invention is directed to isolated DNA molecules which encode Tumor Necrosis Factor (TNF) Binding Protein II (TBP-II) (page 1, lines 2-6). The protein encoded by the DNA of the present invention was initially isolated from human urine and was found to have the ability of selectively inhibiting the cytotoxic effect of TNF (paragraph bridging pages 6 and 7). Under certain conditions it can also act as a carrier for TNF and thus maintain its prolonged beneficial effects (see page 6, lines 13-21, and Example 9, beginning at page 33).

This naturally occurring protein TBP-II, which was isolated from the urine, was found to include the following partial amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis (see page 7, lines 13-15).

The TBP-II encoded by the DNA of the present invention derived from human urine concentrate showed an apparent molecular weight of 30 kD in reducing SDS-PAGE analysis (page 7, lines 2-3).

The DNA of the present invention may also encode active fractions of TBP-II provided the fraction has the ability to inhibit the cytotoxic effect of TNF (see page 15, lines 11-17).

The present claims are drawn to the isolated DNA molecules which encode the newly discovered TBP-II protein and active fragments thereof as well as replicable expression vehicles containing such DNA, host cells transformed with the replicable expression vehicle and processes for producing TBP-II by culturing such a transformant host cell (see page 8, lines 18-23, and claims 11-14 as originally filed).

One claim directed to the TBP-II protein was officially found to be allowable by the examiner in charge of the parent application. The claims drawn to the TBP-II protein in the parent application, 07/930,443, are now involved in an interference proceeding with the claims of U.S. patent 5,344,915.

## THE PRIOR ART

The only prior art rejection in this case appearing in the final rejection of February 26, 1999, was withdrawn by the Advisory Action of August 20, 1999. Thus, there is no prior art which requires discussion in the present brief.

## THE REJECTIONS

The rejection of claims 11-13 and 46-49 under 35 USC 112, first paragraph, as appearing in paragraph 17 of the final rejection was withdrawn in paragraph 2 of the Advisory Action of

August 20, 1999. The rejection of claims 35, 43 and 44 under 35 USC 112, first paragraph, as appearing in paragraph 18 of the final rejection was withdrawn in paragraph 3 of the Advisory Action of August 20, 1999. The rejection of claims 11-13, 35-38, 43, 44 and 46-49 under 35 USC 102(e) as appearing in paragraph 21 of the final rejection was withdrawn in paragraph 5 of the Advisory Action of August 20, 1999. Thus, the only rejection remaining in this case for review in the present appeal is the rejection in paragraph 19 of the final rejection which was repeated in paragraph 4 of the Advisory Action of August 20, 1999. The examiner's restatement of the rejection in this Advisory Action and his comments in response to applicants' arguments, which were not deemed persuasive, are as follows:

> Claims 11-13, 35-38, 43, 44, 46-49, 51 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.
>
> The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the ... claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed DNAs and molecules containing said DNAs.

The instant claims encompass an isolated DNA molecule or vectors or host cells which contain said DNA wherein said DNA encodes a protein consisting of naturally occurring TBP-II. There is no disclosure in the specification of an intact DNA sequence which encodes said molecule. There is no disclosure in the specification of any DNA sequence which encodes the claimed DNA. The claimed molecule recites physical features of a TBP-II protein and the amino acid sequences of a 10-13 amino acid sequence of the N terminal of a molecule that contains at least 250 amino acids. There is no disclosure in the specification of any DNA sequence which encodes the claimed molecule. In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398,1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. In the instant case, the specification has not provided even a single DNA sequence which encodes the claimed DNA. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials ... conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed

to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

Regarding applicants comments in the instant amendment about the criterion C(2) from the interim written description guidelines, the following comments are made. The particular paragraph from C(2) which applicant quotes on page 14 of the instant amendment indicates that in order to meet the written description requirement the characteristics of the claimed invention need to be described "in such full, clear concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention". In the instant application, while applicant has disclosed information and methods to obtain the claimed nucleic acid sequence, applicant was clearly not in possession of the claimed invention at the time the instant application was filed. There is no disclosure in the specification of isolated nucleic acids encoding the molecule recited in the claims.

Regarding the particular example from the interim written description guidelines which applicant quotes in page 15 of the instant amendment, said example differs from the instant application in that the example discloses a scenario wherein the applicant was in physical possession of the claimed molecule. In order to know that said molecule had the particular characteristics disclosed in said example, the molecule was isolated and demonstrated to have said characteristics. Therefore, applicant had physical possession of said molecule. It would be impossible to know the restriction and/or nuclease cleave sites without knowing the intact sequence of said nucleic acid or without having physically isolated the nucleic acid and empirically determined the information. In the case of the instant application, applicant has not demonstrated possession of the claimed invention because while applicant has disclosed a method for isolating said molecule, the molecule was not isolated. Similarly, regarding the enzyme example listed in page 16 of the instant amendment, in order to determine the various physical properties recited in said claim, it was necessary to have already obtained and possessed said molecule. In the case of the instant application, applicant has not demonstrated possession of the claimed invention because while applicant has disclosed a method for isolating said molecule, the molecule was not isolated. Thus, the instant claims do not meet the criterion section C(2) from the interim written description guidelines. Regarding applicants theory that disclosure of a protein provides written description of the nucleic acid, there is no disclosure in the instant application of the amino acid sequence of TBP-II.

Regarding applicants comments in the instant amendment about University of California v. Eli Lilly, there is still no disclosure in the specification of any nucleic acid encoding the scope of the claimed invention (eg. a nucleic

acid encoding TBP-II). There is also no disclosure in the specification of the amino acid sequence of intact TBP-II. While the specification discloses N-terminal amino acid sequence data indicating a possible partial amino acid sequence of 31 amino acids of TBP-II, said peptide contains at least 250 amino acids, wherein the identity of the vast majority of said amino acids has not been disclosed in the specification. In University of California v. Eli Lilly, the court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, Id. at 1240. In the instant case, the specification has not provided even a single DNA sequence which encodes the claimed DNA. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials ... conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Regarding applicants comments that TBP-II protein is disclosed in the specification and the intact amino acid sequence of TBP-II could

be obtained using the methods disclosed in the specification, this is not the issue under consideration. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials ... conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Clearly, in the instant application, the inventor is unable to envision the detailed constitution of a nucleic acid so as to distinguish it from other materials because the sequence of the claimed nucleic acid was not known to the inventors at the time of the filing date of the instant application. Regarding applicants comments about the TBP-II protein, none of the claims of the instant invention are drawn to TBP-II protein. The claims under consideration are drawn to nucleic acids. The possession of an isolated protein in itself provides no written description of the identity of the nucleic acid encoding said protein in the absence of the complete amino acid sequence of said protein. Applicants response recites "Once the complete amino acid sequence is known, all contiguous DNA sequences which encode such a protein are known in view of the known rules of the genetic code.". However, the complete amino acid sequence of TBP-II is not disclosed in the instant application. The instant application merely recites methods that could be potentially used to elucidate the nature of said sequence. In the absence of the disclosure of the claimed nucleic acid in the specification or the complete amino acid sequence of TBP-II there is no written description of the scope of the claimed invention. Regarding applicants comments that University of California v. Eli Lilly only applies to "genes" per se, this not stated in University of California v. Eli Lilly. In fact, in University of California v. Eli Lilly the court clearly states that:

*An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.*

In the instant application, applicants has provided a plan and potential method for isolating the claimed nucleic acids, but have provided no written description of said nucleic acids.

## ISSUE

The following issue is presented in this appeal:

Is there adequate written description for a claim covering all DNA sequences which encode a novel isolated protein defined by a partial amino acid sequence and other characterizing features?

## GROUPING OF THE CLAIMS

All of the claims stand or fall together

## ARGUMENT

The Patent Specification as Filed Describes the Claimed DNA in Sufficient Detail that One Skilled in the Art Can Reasonably Conclude that the Inventor Had Possession of the Claimed DNA

Applicant's position with respect to the written description rejection can be thumbnailed by the following syllogism.

1. The specification contains adequate written description for the TBP protein.

2. The complete amino acid sequence of a protein is an inherent property of an isolated protein. Therefore, even though the complete amino acid sequence was not explicitly disclosed, applicant was inherently in possession of the complete amino acid sequence.

3. Once one has demonstrated possession of the complete amino acid sequence, the genetic code automatically puts one in possession of all DNA sequences encoding that amino acid sequence. QED.

As to the first paragraph of the above syllogism, it is not believed that the examiner disputes the fact that there is written description for the TBP protein in the application as originally filed. It should be noted that during the prosecution of this case the examiner has not refuted this particular part of the syllogism. The examiner states at the beginning of the first full paragraph on page 4 of the Advisory Action of August 20, 1999:

> Regarding applicant's comments that TBP-II protein is disclosed in the specification and the intact amino acid sequence of TBP-II could

> be obtained using the method disclosed in the specification, this is not the issue under consideration.

The first paragraph of the syllogism is consistent with the Revised Interim Guidelines.[1] Section II.3.A.(1)(a)-(c) of these Guidelines states that, for original claims, for each claim drawn to a single species, one must first determine whether the application describes an actual reduction to practice of the claimed invention or if there is evidence of a completed invention by reduction to drawings. Section (c) goes on to state:

> If the application does not describe an actual reduction to practice or reduction to drawings, determine whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention.

Here, with respect to the protein, there was an actual reduction to practice as the protein was actually isolated. Furthermore, the protein was described by a partial amino acid sequence and sufficient other distinguishing identifying characteristics that are sufficiently detailed to show that applicant was in possession of the claimed invention. The fact that the protein was adequately described to comply with the written description requirement is evidenced by the fact that at

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[1] Throughout this brief, "Revised Interim Guidelines" will refer to the "Revised Interim Guidelines for Examination of Patent Applications under the 35 U.S.C. §112, §1 'Written Description' Requirement", published in the Federal Register on December 21, 1999, at 64(244) 71427-71440. A copy of the Revised Interim Guidelines is attached hereto as Appendix B for the convenience of the Board.

least one protein claim was allowed during the prosecution of the parent application 07/930,443, which is now involved in an interference proceeding with the claims of U.S. patent 5,344,915.

With respect to the second paragraph of the above syllogism, reference is made to Ex parte Yamaguchi, 6 USPQ2d 1805, 1807 (BdPatApp&Int 1987), where it states:

> Moreover, it is well settled that from a standpoint of patent law, a compound and all of its properties are inseparable. They are one and the same. *In re Papesch* 50, CCPA 1084, 315 F2d 381, 137 USPQ 43 (1963). In our view, the X-ray diffraction spectrum, like the graphic formulae, the chemical nomenclature, etc., is merely a symbol by which the compounds can be identified, classified and compared.

The same is true for the amino acid sequence of a protein.

See also Ex parte Marsili, 214 USPQ 904 (PTOBdApp 1979) which held that a change in the structural formula of a chemical compound that was adequately described in terms of its characteristics in the original specification did not violate the description requirement. It is also noted that in the Board decision of Ex parte Deuel, 27 USPQ2d 1360, 1363 (BdPatApp&Int 1993), the Board noted the examiner's position that the amino acid sequence is an inherent characteristic of the protein.

In this case, in light of the partial amino acid sequence of the protein and the other characterizing features disclosed, as well as the method for obtaining the protein, one of ordinary skill in the art could obtain the entire amino acid sequence of the protein without undue experimentation.

As to the third paragraph of the syllogism, it is clear that the present DNA claims generically encompass all DNA sequences encoding naturally occurring human TBP-II. As the genetic code provides a direct relationship of amino acid sequences and associated nucleic acid codons, it is a scientific fact that given the complete amino acid sequence of a protein, coupled with knowledge of the genetic code, one is in possession of the genus of all of the DNA sequences which will encode that complete amino acid sequence. In re Deuel, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995), noted that, with the aid of a computer, a person of ordinary skill in the art may even be able to identify all members of the claimed genus. Thus, if one is in possession of the complete amino acid sequence encoded by a claimed DNA sequence, then one is necessarily in possession of the entire claimed DNA genus.

As stated in the Revised Interim Guidelines in the second paragraph of Section I:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Similarly, the last paragraph of Section I reads:

> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.

Thus, it is possession of the claimed invention which is important. The above syllogism establishes that applicant was in

possession of the genus of DNA sequences that encode the single species of naturally occurring human TBP-II. As applicant was in possession of the invention as now claimed, the fundamental factual inquiry necessary to satisfy the written description requirement must be answered in the affirmative.

There is nothing in the case law cited by the examiner which precludes an applicant from claiming the genus of DNA which encodes an adequately disclosed protein. Admittedly, if the present claims were directed to the human cDNA encoding TBP-II, the case law would require a 35 USC 112, first paragraph, written description rejection because it would have been impossible for applicant to envision that single specific sequence which is the cDNA. Thus, even though there is written description in the present specification for the genus of all DNA sequences which encode a given amino acid sequence, there is admittedly no written description for the specific species of the cDNA, and indeed the specific species of the cDNA is not being specifically claimed in the present application. In the case relied upon by the examiner, discussed in detail hereinbelow, the claims being reviewed for compliance with the written description requirement were directed to the cDNA and not to broad DNA claims covering any DNA sequence which encodes the novel protein. Indeed, in the case cited by the examiner, the protein was not novel and therefore a generic DNA claim, such as is presently claimed, would have been obvious.

More specifically, the examiner relies mainly on University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997). While that case relates to the infringement of

two patents, i.e., patents 4,652,525 and 4,431,740 owned by the Regents of the University of California (UC), validity issues relating to the written description requirement of the first paragraph of 35 USC 112 were raised only with respect to the '525 patent. Copies of the front page and claims of these two patents are attached hereto as Appendices C and D. It can be seen that, in the '525 patent, all of the claims are directed to insulin-encoding cDNA, or the reverse transcript of mRNA which encodes insulin, which is synonymous with cDNA. Note that the Federal Circuit in the Lilly case at page 1405 characterizes claims 1 and 2 of the '525 patent as being claims "which *generically* recite cDNA encoding vertebrate insulin, and claim 4, which is directed *generically* to cDNA encoding mammalian insulin" [emphasis original] and that dependent claims 6 and 7 "similarly recite cDNA encoding vertebrate insulin." As to claim 5, the court stated, at pages 1404-1405:

> Claim 5 is directed to a recombinant prokaryotic microorganism modified so that it contains "a nucleotide sequence having the structure of the reverse transcript of an mRNA of a [human], which mRNA encodes insulin.

Thus, the definition of the claimed microorganism is one that requires human insulin-encoding cDNA. The validity of claim 3 was not before the court. Thus, it is very clear that all of the claims being construed for compliance with the written description requirement were claims directed to cDNA, i.e., the naturally occurring sequence which is only one of the myriad of possible sequences which encode human insulin due to the degeneracy of the genetic code. Therefore, the holdings in the Lilly case which

require that the sequence of the cDNA be known before that cDNA can be in the possession of the inventors so as to satisfy the written description requirement, are all related to the specific situation before the court in which all that is being claimed is cDNAs, either a cDNA of a single species or a genus of cDNAs of a plurality of animal species.

In the Advisory Action of August 20, 1999, in response to applicant's previous arguments that the Lilly case applied only to cDNAs *per se*, the examiner refers to page 1404 of Lilly where it states:

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention.

However, when the DNA claim is written broadly so as to include all DNA which encodes a particular amino acid sequence, the description of the amino acid sequence or sufficient characterizing information to establish that applicant was in possession of a novel protein, is sufficient to satisfy the requirement for a precise definition. Indeed, the examiner himself states at page 6 of the Advisory Action:

> In the absence of the disclosure of the claimed nucleic acid in the specification, or the complete amino acid sequence of TBP-II there is no written description of the scope of the claimed invention. [Emphasis added]

Thus, the examiner appears to admit that if applicant were in possession of the complete amino acid sequence of TBP-II, then

applicant would automatically be in possession of the claimed nucleic acid sequence which anyone of ordinary skill in the art could write as a formula once the complete amino acid sequence is known. Indeed, reference is made to claim 5 of the '740 patent involved in the Lilly case in which such a DNA sequence broad enough to encompass all DNAs which encode human proinsulin is set forth. Such a formula can readily be prepared for any given amino acid sequence without any knowledge of the naturally occurring cDNA.

Reference is also made to footnote 13 of the Revised Interim Guidelines which explicitly states:

> [a] genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids ... .

Here, applicant readily admits that the specification does not contain a complete amino acid sequence of TBP-II. However, it does disclose a partial amino acid sequence and sufficient other characterizing features to establish that applicant was in possession of the protein. Indeed, applicant had isolated the protein. The written description requirement was satisfied for the protein as is evidenced by the allowability of at least one protein claim in the parent application. As the complete amino acid sequence of a protein is an inherent property of an adequately described protein which is in possession of the applicant and a genetic code table can correlate any amino acid sequence with a genus of coding nucleic acids, it must necessarily follow that adequate written description of a protein is

inherently an adequate written description of a broad DNA claim which encompasses all nucleotide sequences which encode that protein.

There is nothing in the Revised Interim Guidelines which mandates a rejection of the present claims under the written description requirement. Indeed, in the response to comment 6 at page 71429 of the Federal Register notice, the material accompanying these Guidelines makes clear that the Revised Interim Guidelines do not impose a *per se* requirement for reduction to practice in any technology to satisfy the written description requirement. The discussion goes on to state:

> However, the Federal Circuit has recognized that in some instances an inventor may only be able to establish a conception (and therefore possession) by pointing to a reduction to practice through a successful experiment. ... In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention.

Here, while applicant may not have reduced to practice a specific DNA, applicant has reduced to practice the protein. Applicant has possession of the protein and has provided adequate written description of the protein. The complete amino acid sequence of the protein is an inherent property of the protein. Because the formula of all DNA which encompass that amino acid sequence is dictated by the genetic code, i.e., is a fixed formula, the DNA sequence is as much an inherent property of the adequately

described protein which has been reduced to practice as is the complete amino acid sequence thereof. Therefore, there is no actual uncertainty that undermines the specificity of the inventor's idea of the invention, such as would require an actual reduction to practice of a DNA before an applicant can be in possession thereof.

The statement in Section II.A.3 at the right column of page 71435 of the Federal Register notice is also applicable where it states:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Such sufficiently detailed relevant identifying characteristics have been provided in the present specification for the protein. As the complete amino acid sequence of the protein is an inherent characteristic of the protein and as the formula for DNA which encodes the complete amino acid sequence is a fixed formula determined by the genetic code, such DNA formula is also an inherent characteristic of the adequately described protein.

Furthermore, the claims effectively include a partial nucleic acid sequence. All of the present claims recite at least 10 amino acid residues of the protein encoded by the DNA. Thus, at least 30 nucleotides of the DNA are disclosed. Regardless of the fact that the DNA molecule of the present invention is much

longer than 30 nucleotides, this is an important unique bit of characterizing information. This piece of nucleotide structure, in conjunction with the characterizing information that the DNA encodes a protein having the ability to inhibit the cytotoxic effects of TNF, provides sufficient relevant identifying characteristics to comply with the criteria of the above-quoted portion of the Revised Interim Guidelines.

The same paragraph of the Revised Interim Guidelines goes on to state:

> If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

This sentence further supports the conclusion reached by the syllogism set forth hereinabove. Accordingly, for the reasons discussed in detail hereinabove, possession of a novel protein and a written description thereof sufficient to comply with the written description requirement of the first paragraph of 35 USC 112 inherently places one in possession of the formula of all DNA which encodes that protein. As the complete amino acid sequence of that protein is an inherent property of the protein and the generic DNA sequence which encodes that amino acid sequence is directly correlatable therewith by means of a genetic code table, a holding that the present claims comply with the written description requirement would be fully consistent with the newly issued Revised Interim Guidelines. Reversal of the examiner and withdrawal of this rejection are therefore respectfully urged.

**CONCLUSION**

The claims as submitted are believed to truly set forth the inventive concept of the present invention and to fully comply with the written description requirement of the first paragraph of 35 USC 112. Accordingly, reversal of the examiner and allowance of claims 11-13, 35-38, 43, 44, 46-49 and 51 are earnestly solicited.

Respectfully submitted,

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## APPENDIX A

11. An isolated DNA molecule comprising a contiguous nucleotide sequence coding for a protein consisting of naturally occurring human Tumor Necrosis Factor (TNF) Binding Protein II, herein designated TBP-II, said TBP-II including the amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis, said protein having the ability to inhibit the cytotoxic effect of TNF, wherein said naturally occurring TBP-II protein is the same as that protein having the ability to inhibit the cytotoxic effect of TNF which, after being purified by subjecting a crude protein recovered from a dialyzed concentrate of human urine to affinity chromatography on a column of immobilized TNF, elutes from a reversed-phase high pressure liquid chromatography column as a single peak in a fraction corresponding to about 31% acetonitrile and shows a molecular weight of about 30 kDa when measured by SDS-PAGE under reducing conditions.

12. A replicable expression vehicle comprising the DNA molecule of claim 11 and capable, in a transformant host cell, of expressing said protein.

13. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 12.

35. An isolated DNA molecule in accordance with claim 51, comprising

(1) the nucleotide sequence coding for a naturally occurring human Tumor Necrosis Factor (TNF) binding protein (TBP-II) having the following characteristics:

i. includes the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly- Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis; and

ii. the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells, or

(2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells.

36. An isolated DNA molecule comprising

(1) the nucleotide sequence coding for a naturally occurring human Tumor Necrosis Factor (TNF) binding protein (TBP-II) having the following characteristics:

i. includes the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly- Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis; and

ii. the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells; and

iii. a molecular weight of about 30kd in reducing SDS-PAGE analysis, or

(2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells.

37. A replicable expression vehicle comprising the DNA molecule of claim 51 and capable, in a transformant host cell, of expressing said protein.

38. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 37.

43. A replicable expression vehicle comprising the DNA molecule of claim 35 and capable, in a transformant host cell, of expressing said protein.

44. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 43.

46. An isolated DNA molecule comprising (1) a contiguous nucleotide sequence coding for a protein consisting of naturally occurring human Tumor Necrosis Factor (TNF) Binding Protein II, herein designated TBP-II, said TBP-II including the amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in

the portion of the protein sequenced by N-terminal sequence analysis, said protein having the ability to inhibit the cytotoxic effect of TNF, wherein said naturally occurring TBP-II protein is the same as that protein having the ability to inhibit the cytotoxic effect of TNF which, after being purified by subjecting a crude protein recovered from a dialyzed concentrate of human urine to affinity chromatography on a column of immobilized TNF, elutes from a reversed-phase high pressure liquid chromatography column as a single peak in a fraction corresponding to about 31% acetonitrile and shows a molecular weight of about 30 kDa when measured by SDS-PAGE under reducing conditions, or (2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF.

47. An isolated DNA molecule in accordance with claim 51, wherein said nucleotide sequence is the sequence of (2).

48. A replicable expression vehicle comprising the DNA molecule of claim 47 and capable, in a transformant host cell, of expressing said protein.

49. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 48.

51. An isolated DNA molecule comprising

(1) a contiguous nucleotide sequence coding for a naturally occurring human Tumor Necrosis Factor (TNF) binding protein (TBP-II) having the following characteristics:

(a) includes the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis; and

(b) has the ability to inhibit the cytotoxic effect of TNF; or

(2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF.

roger\briefs\wall5b.clm

FOR FURTHER INFORMATION CONTACT: Dan Waldeck, Pacific Fishery Management Council; (503) 326–6352.

SUPPLEMENTARY INFORMATION: The primary purpose of the work session is to draft sections of the fishery management plan and related documents for highly migratory species fisheries off the West Coast.

Although non-emergency issues not contained in the HMSPDT meeting agenda may come before the HMSPDT for discussion, those issues may not be the subject of formal HMSPDT action during these meetings. HMSPDT action will be restricted to those issues specifically listed in this notice and any issues arising after publication of this notice that require emergency action under section 305(c) of the Magnuson-Stevens Fishery Conservation and Management Act, provided the public has been notified of the HMSPDT's intent to take final action to address the emergency.

### Special Accommodations

The meeting is physically accessible to people with disabilities. Requests for sign language interpretation or other auxiliary aids should be directed to Mr. John Rhoton at (503) 326–6352 at least 5 days prior to the meeting date.

Dated: December 16, 1999.

Bruce C. Morehead,

*Acting Director, Office of Sustainable Fisheries, National Marine Fisheries Service.*

[FR Doc. 99–33066 Filed 12–20–99; 8:45 am]

BILLING CODE 3510–22–F

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## DEPARTMENT OF COMMERCE

## Patent and Trademark Office

[Docket No. 991027288–9288–01]

RIN 0651–AB10

## Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description" Requirement; Request for Comments

AGENCY: Patent and Trademark Office, Commerce.

ACTION: Notice and request for public comments.

SUMMARY: The Patent and Trademark Office (PTO) requests comments from any interested member of the public on the following Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement (Revised Interim Guidelines). These Revised Interim Guidelines will be used by PTO personnel in their review of patent applications for compliance with the "written description" requirement of 35 U.S.C. § 112, ¶ 1. This revision supersedes the Interim Written Description Guidelines which were published contemporaneously in both the Federal Register and Official Gazette at 63 FR 32,639 (June 15, 1998) and 1212 O.G. 15 (July 7, 1998), respectively. This revision reflects the current understanding of the PTO regarding the written description requirement of 35 U.S.C. 112, ¶ 1 and is applicable to all technologies.

DATES: Written comments on the Revised Interim Guidelines will be accepted by the PTO until March 22, 2000.

ADDRESSES: Written comments should be addressed to Box 8, Commissioner of Patents and Trademarks, Washington, DC 20231, marked to the attention of Stephen Walsh, or to Box Comments, Assistant Commissioner for Patents, Washington, DC 20231, marked to the attention of Linda S. Therkorn. Alternatively, comments may be submitted to Stephen Walsh via facsimile at (703) 305–9373 or by electronic mail addressed to "stephen.walsh@uspto.gov" or to Linda Therkorn via facsimile at (703) 305–8825 or by electronic mail addressed to "linda.therkorn@uspto.gov."

FOR FURTHER INFORMATION CONTACT: Stephen Walsh by telephone at (703) 305–9035, by facsimile at (703) 305–9373, by mail to his attention addressed to Box 8, Commissioner of Patents and Trademarks, Washington, DC 20231, or by electronic mail at "stephen.walsh@uspto.gov"; or Linda Therkorn by telephone at (703) 305–8800, by facsimile at (703) 305–8825, by mail addressed to Box Comments, Assistant Commissioner for Patents, Washington, DC 20231, or by electronic mail at "linda.therkorn@uspto.gov."

SUPPLEMENTARY INFORMATION: The PTO requests comments from any interested member of the public on the following Revised Interim Guidelines. As of the publication date of this notice, this revision will be used by PTO personnel in their review of patent applications for compliance with the "written description" requirement of 35 U.S.C. 112, ¶ 1. Because this revision governs internal practices, it is exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A).

Written comments should include the following information: (1) Name and affiliation of the individual responding, and (2) an indication of whether the comments offered represent views of the respondent's organization or are respondent's personal views. If you believe the PTO should further amend these revised interim guidelines before they are made final, you should include the following information in your comments: (1) The rationale supporting the proposal, including the identification of applicable legal authority; and (2) a description of the potential benefits and drawbacks of adopting the proposal. The PTO is particularly interested in comments relating to the following topics: (1) The accuracy of the methodology, (2) the legal analysis in the guidelines, and (3) relevant factors to consider in determining whether the written description requirement is satisfied.

Parties presenting written comments are requested, where possible, to provide their comments in machine-readable format in addition to a paper copy. Such submissions may be provided by electronic mail messages sent over the Internet, or on a 3.5" floppy disk formatted for use in a Macintosh, Windows, Windows for Workgroups, Windows 95, Windows 98, Windows NT, or MS–DOS based computer.

Written comments will be available for public inspection on or about April 19, 2000, in Suite 918, Crystal Park 2, 2121 Crystal Drive, Arlington, Virginia. In addition, comments provided in machine readable format will be available through the PTO's Website at http://www.uspto.gov.

### Discussion of Public Comments

Comments were received from 13 individuals and 16 organizations in response to the Request for Comments on the Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement published contemporaneously in the Federal Register and Official Gazette at 63 FR 32,639 (June 15, 1998) and 1212 O.G. 15 (July 7, 1998), respectively; and the Extension of Comment Period and Notice of Hearing published at 63 FR 50887 (September 23, 1998) and 1214 O.G. 180 (September 29, 1998). The written comments and the testimony at the public hearing have been carefully considered.

### Overview of Comments

The majority of comments favored issuance of written description guidelines, with revisions. Several major issues arose in the oral testimony and written comments submitted in response to the Interim Guidelines on the Written Description Requirement with respect to the scope of the Guidelines, the method of analysis, and the content of the examples. In view of

the comments and testimony received, the Guidelines have been rewritten in a technology neutral manner which is broadly applicable to all areas of technology and to all types of claims (original, new, or amended, and product, process, or product-by-process). Furthermore, the examples have been removed from the Guidelines and examples addressing a broad range of technologies will be incorporated into examiner training materials. Revised Interim Guidelines are being issued for a second round of Notice and Comment because the form and content of the Guidelines are sufficiently different from the previous Guidelines that additional public comment is desired.

The Extension of Comment Period and Notice of Hearing published at 63 FR 50887 (September 23, 1998) and 1214 O.G. 180 (September 29, 1998) asked for comments regarding the patentability of Expressed Sequence Tags (ESTs). Many comments took this opportunity to heavily criticize the patentability of ESTs, grounding their arguments in fairness and policy issues. Many comments also expressed the opinion that ESTs lacked the utility, enablement, and written description necessary to satisfy title 35 of the U.S. Code. The Revised Interim Guidelines are not the appropriate vehicle to fully address the patentability of ESTs. In view of comments and testimony with respect to ESTs and the enablement and utility requirements, the Office is revising the Utility Guidelines as published at 60 FR 36263 (July 14, 1995), and will also be revising the examiner training material with regard to both the utility and enablement requirements. Comments pertaining to the utility and enablement requirements will be addressed in the notice revising the Utility Guidelines. Responses to the comments germane to the written description requirement are set forth below.

Responses to Specific Comments

(1) *Comment:* Several comments criticized the Guidelines for failing to set out a general, systematic examination of the case law on written description. Comments mentioned *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), in particular as important for summarizing the state of the law as the Federal Circuit sees it. Other comments particularly urged a general analysis of case law as it pertains to written description for chemical compounds, and criticized the fact that the Guidelines relied heavily on only three recent cases. *Response:* The suggestion to provide a general, systematic legal analysis has been adopted. The Revised Interim Guidelines are grounded more broadly than the three cases heavily relied upon in the original Interim Guidelines, and cases dealing with a variety of arts are relied upon.

(2) *Comment:* The comments were equally divided with respect to the issue of whether the Guidelines should be broadly applicable to all technologies or limited to biotechnology, DNA claims, or unpredictable arts. Two of the comments urging broad applicability stated that the law should be articulated in a clear and technology neutral fashion, and several comments urged that examples and training materials should illustrate application of the Guidelines in a diverse range of technologies. One comment suggested that applications in which written description problems are likely to arise should be identified generically, rather than requiring a written description analysis in each application. *Response:* The suggestion to cover all technologies and to articulate the law in a clear and technology neutral fashion has been adopted. While a written description analysis is required in each case, the Revised Interim Guidelines clearly specify when a written description issue is most likely to arise, and—for most applications—the Revised Interim Guidelines will quickly lead the examiner to determine that, at least for original claims, the written description requirement has been met. The Revised Interim Guidelines avoid narrowing the application of the written description requirement to a single art, and the examiner training materials will illustrate application of the revision in various technologies.

(3) *Comment:* While the majority of comments supported the Interim Guidelines, eight comments opposed their issuance. Some of those opposing the guidelines argued that the decision in *Regents of the University of California* v. *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998), is a drastic departure from legal precedent and PTO practice. In particular, two comments suggested that the Interim Guidelines should be replaced by Revised Interim Guidelines, and one comment recommended that final Guidelines be deferred until the U.S. Court of Appeals for the Federal Circuit or the U.S. Supreme Court hands down decisions that elaborate, construe, modify, or overrule *Eli Lilly* and/or decide related issues not dealt with by that case. See Comments (5) and (9) for more opposing comments. *Response:* This revision is based on the Office's current understanding of the law and is believed to be fully consistent with binding precedent of the U.S. Supreme Court and the U.S. Court of Appeals for the Federal Circuit. Guidelines are necessary in this area to promote uniformity and consistency in the examination process. The suggestion to issue Revised Interim Guidelines for a second round of Notice and Comment has been adopted. The revision is written in a technology neutral manner, and the form is sufficiently different from the previous guidelines that additional public comment is desired.

(4) *Comment:* Six comments were in favor of including process and product-by-process claims in the analysis, whereas one comment was opposed. One comment criticized the Guidelines for failing to acknowledge the "safe harbor" product-by-process type claim noted in *Fiers* v. *Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993), and *Amgen Inc.* v. *Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). One comment observed that process and product-by-process claims tend not to implicate many written description issues, and it may be useful to point out possible enablement deficiencies for such claims. Two comments suggested that the Guidelines should distinguish between claims to processes whose patentability depends on the compositions used in them, as opposed to those where patentability rests in the steps of the process itself. *Response:* The suggestion to address process and product-by-process claims has been adopted. Furthermore, the training materials will analyze claims wherein the patentability depends on the compositions used therein, as well as those where the patentability rests in the process steps themselves. Enablement issues raised by process and product-by-process claims are outside the scope of these Revised Interim Guidelines.

(5) *Comment:* While one comment stated that the Guidelines correctly present the relationship between written description and enablement, a number of comments dispute that the statute actually has a written description requirement distinct from the enablement requirement. One comment requested that the PTO refrain from issuing any Guidelines in this area until the U.S. Supreme Court rules on the Federal Circuit's present position on written description. Several comments urged the PTO to announce that it will not follow the court decisions applying the separate written description requirement, while others observed that the PTO and the practitioners must nevertheless follow the case law. Some of these comments urged the PTO to

withdraw the Guidelines on the grounds that they are premature because the case law has not developed sufficiently. Others urged the PTO to limit application of the Guidelines to the narrow subject matter of the *Fiers*, *Amgen*, and *Eli Lilly* cases. *Response:* A separate written description requirement has long been a part of the U.S. patent law. *See, e.g., In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967). The Federal Circuit has recognized the distinct and separable nature of this requirement. *See Vas-Cath*. Although the interpretation of the law is always evolving, the PTO is obliged to follow the law as currently interpreted by the court. As noted above, the suggestion to limit the application of the Revised Interim Guidelines to certain subject matter has not been adopted.

(6) *Comment:* While several of the comments stated that the Guideline's explanation of the purpose of the written description requirement is accurate, a number of comments suggested that the concept of "possession" should be more fully explained or developed. One comment urged that the meaning of "possession of the invention" is different for written description than enablement, whereas another observed that an "in possession of the invention" test for compliance with the written description requirement does not appear in 35 U.S.C. 112, and its definition and application are not clearly stated in the Federal Circuit cases to date. Another comment urged that descriptive attributes which provide proof of written description should include evidence typically provided to prove a complete and enabling conception. One comment stated that the meaning of "has invented" is unclear and queried if actual reduction to practice is required. The same comment asked for clarification on what kind of description equates with possession of a claimed species. One comment stated that a question left unanswered in the Guidelines is that if one has "made" an invention, is one necessarily in possession of it, or are there some further criteria? Two comments observed that physical possession is not necessary: one must have complete conception of the invention in mind. These comments suggested that the possession analysis incorporate the Supreme Court's statements in *Pfaff* v. *Wells Electronics, Inc.*, 525 U.S. 55, 48 USPQ2d 1641 (1998) (the word "invention" must refer to a concept that is complete: one can prove that an invention is complete and ready for patenting before it has been reduced to practice). One of these comments elaborated that the doctrine of simultaneous conception and reduction to practice should remain applicable to only a very small number of cases, including biotechnology cases. *Response:* The Revised Interim Guidelines expand the explanation of possession by discussing decisions that offer some guidance as to how possession may be shown. The concepts in *Pfaff* v. *Wells Electronics* that are pertinent to an analysis of compliance with the written description requirement have been incorporated in this revision. At this time, the Federal Circuit has not indicated that reduction to practice is necessary for conception or written description of a biotechnological invention. The Office does not intend to impose a written description requirement that is more robust than that set forth by the courts. Accordingly, the Revised Interim Guidelines do not impose a *per se* requirement for reduction to practice in any technology to satisfy the written description requirement. However, the Federal Circuit has recognized that in some instances an inventor may only be able to establish a conception (and therefore possession) by pointing to a reduction to practice through a successful experiment. *See Amgen Inc.* v. *Chugai Pharmaceutical Co.*, 927 F.2d at 1206, 18 USPQ2d at 1021. In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co.* v. *Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention. *Id.*

(7) *Comment:* Other comments on "possession" urged that possession is to be evaluated by looking to the claims; that the possession question is to be assessed as set forth in *In re Alton*, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996); and that compliance must be assessed on a case-by-case basis given that the question of compliance with the written description requirement is one of fact. One comment stated that the test should be whether the inventor had envisioned the embodiments, not that one of skill in the art can now envision the embodiments. Another comment stated that the Guidelines should take a position with regard to their application to the analysis of declarations submitted under 37 CFR 1.131. *Response:* The Revised Interim Guidelines require the examiner to determine whether there is sufficient written description to inform a skilled artisan that the applicant was in possession of the claimed invention as a whole at the time the application was filed. The revision also indicates that compliance with the written description requirement is a question of fact which must be resolved on a case-by-case basis. While this revision addresses the analysis of possession only in the context of the written description requirement, similar principles apply in determining whether an inventor has met his or her burden of demonstrating possession of the claimed invention in an affidavit or declaration submitted under 37 CFR 1.131.

(8) *Comment:* Several comments suggested that the Guidelines should address questions of support for claims added or amended by the applicant during prosecution (or during an interference). Two comments suggested that the Guidelines should address the "omitted element" prong of the written description requirement. One comment indicated the Guidelines should harmonize chemical and nonchemical case law on when an applicant may amend to broaden or change a definition based on an original disclosure. Another comment stated that the Guidelines should acknowledge that it is proper to amend the claims to excise prior art. *Response:* The suggestions to address questions of support for new or amended claims and to address the "omitted element" test have been adopted.

(9) *Comment:* Several comments indicated that case law such as *In re Koller*, 613 F.2d 819, 204 USPQ 702 (CCPA 1980), hold that original claims constitute their own written description, or that a statement in *ipsis verbis* is a sufficient description, and that those cases should be adhered to. Three comments pointed out that the Guidelines fail to distinguish between original claims and added/amended claims, arguing that the original claim doctrine should exempt originally filed claims from further requirements. *Response:* The Revised Interim Guidelines emphasize that a description as filed is presumed to be adequate, unless or until the examiner introduces sufficient evidence or technical reasoning to the contrary. The original claim doctrine continues to be viable, but the court has indicated that every claim must be supported by sufficient

evidence of possession, and that, under certain circumstances, claim language may not provide an adequate written description of itself. There are no *per se* rules, since the analysis must be done on a case-by-case basis. While original claims have an initial presumption of descriptive support, the applicant should show support for new or amended claims. *See, e.g.*, Manual of Patent Examining Procedure (MPEP) §§ 714.02 and 2163.06 (7th Ed., July 1998) ("Applicant should * * * specifically point out the support for any amendments made to the disclosure.").

(10) *Comment:* One comment indicated that written description problems may arise where there is an inadequate description or demonstration of possession of a genus or where there is an improper genus (no common structure and function that is linked to the practical utility disclosed by the specification). Another comment stated that the Guidelines should address the informational nature of nucleic acid sequences and amino acid sequences. One comment urged that "[a] written description of a genus is sufficient when it is described in enough detail that possession is understood," and that the number of species relates more to enablement. *Response:* The Revised Interim Guidelines indicate that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. The revision does not require a particular number of species to support a genus, but rather requires that the species adequately described be representative of the claimed genus.

(11) *Comment:* A comment urged that the Guidelines should explicitly state that the maturation of the technology will increase the understanding of one skilled in the art, and ease the predictable scope of the claimed invention beyond the exemplified embodiments, as recognized in the applicant's specification. *Response:* The Revised Interim Guidelines emphasize that in a mature art with a high level of knowledge and skill, less evidence of possession is required.

(12) *Comment:* One comment objected to the requirement for an assessment of predictability as a touchstone for written description. The comment described this inquiry as new and lacking case law support. Several comments stated that predictability is an inquiry relating to the enablement requirement, but not to the written description requirement. Others commented generally that the Guidelines conflate what should be separate enablement and written description analyses. On the other hand, at least one comment stated that the distinctions between these elements converge when lack of enablement results from undue breadth of claims. One comment stated that a review of the application is insufficient to establish the level of predictability in an art. Another queried if the review is to be done after a search in the art and assessment of the art. Another comment stated that the lack of guidance for distinguishing between predictable and unpredictable areas within the field of biotechnology leads to confusion. *Response:* The Revised Interim Guidelines reduce the emphasis on predictability because of the confusion with enablement. Instead, the Guidelines emphasize the knowledge in the art and the skill of the practitioner considered in the totality of the circumstances. With respect to the comment regarding biotechnology, this sliding scale will permit broader claims as the knowledge and skill in this art improve. The Guidelines discuss how the general knowledge in the art may be relied on as evidence of how much description may be needed in particular cases.

(13) *Comment:* Several comments criticized the methodology of the Guidelines because the analytic steps set out by the court in *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971) (first determine what the claims cover, then review the specification for support) were reversed. *Response:* The Revised Interim Guidelines restate the analytic sequence so it is clearly consistent with *In re Moore*. The revision also makes it clear that each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. *See, e.g., In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

(14) *Comment:* One comment suggested that the Guidelines should provide more instruction on the different amount of description needed to support an essential feature of an invention in contrast to a nonessential feature. The comment explained that contrasting the amount of description needed to support a novel or nonobvious feature of an invention with the amount of description needed for features of an invention that were known in the prior art would be helpful. *Response:* The Revised Interim Guidelines distinguish between novel and old elements in a claim to clarify that the amount of written support needed in an application can vary depending on the general knowledge that was readily available in a particular art.

(15) *Comment:* One comment criticized the analysis for setting out conclusions before the analytic method and for distorting or bypassing the analysis. The same comment said that some of the examples yield illogical results. *Response:* The examples have been deleted from the Guidelines, and the analytical method has been clarified.

(16) *Comment:* The Guidelines were heavily criticized in ten comments for overemphasizing the importance of the preamble and for indicating that generic preamble terms such as "nucleic acid" would need less descriptive support than narrower terms such as "cDNA." One comment objected to the proposition that one may have an adequate written description of a genus of DNA when one does not disclose what gene product the DNA encodes and what that gene product does. This comment recommended deletion of the example bridging F.R. 32640–41 ("a gene comprising SEQ ID NO: 1") as inconsistent with the rest of the Guidelines. *Response:* The Revised Interim Guidelines clarify that the examiner must consider the claim as a whole and that the preamble may be a limitation of the claim. Preamble language is discussed in the context of determining what the claim as a whole encompasses within its scope. However, the Revised Interim Guidelines maintain that any term may trigger a need for more descriptive support because of usage or context. The revision clarifies that during examination claim terms are given their broadest reasonable interpretation consistent with the specification. *See In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997). The examples have been removed from the text of the revision.

(17) *Comment:* Four comments objected to the Guidelines' definitions for the terms gene, mRNA, and cDNA, stating that the art often refers only to the coding portion of the molecules and does not necessarily imply the presence of regulatory elements or recite specific structures. One comment further indicated that adoption of the PTO's new definition of these terms for purposes of written description considerations could potentially destabilize the economic infrastructure of the biotechnology community because innumerable patents have issued claiming such molecules without regard to the PTO's new interpretation of claim language. The Guidelines were said to use two inconsistent meanings for the term gene that differed in scope and confused the distinction between

genus and species. *Response:* The Revised Interim Guidelines no longer define the term "gene."

(18) *Comment:* One comment indicated that the PTO has the opportunity to emphasize the written description requirement as an anti-submarine patent device; this comment and another observed that two parties could obtain claims which would be almost identical in scope in hindsight, based on completely different paths to the claim. *Response:* In *Hyatt* v. *Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998), the Federal Circuit addressed the submarine patent issue in finding that the appellant's parent application lacked written descriptive support for a later added claim. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation." *Id.*

(19) *Comment:* A comment stated that the Guidelines give too much emphasis to claim structure, as if the claim is the sole source of the written description. Another comment had a different view, stating that the Guidelines fail to focus on the invention being claimed, and noting that in some circumstances, failure to provide the structure of a gene, enzyme, etc. should not result in finding that a claim containing it fails to meet the written description requirement. *Response:* The Office gives a claim its broadest reasonable interpretation during examination. If the claim taken as a whole requires a limitation not set forth in the original disclosure it may raise an issue of lack of proper written description. As noted in *In re Hiniker Co.*, 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998), "the name of the game is the claim."

(20) *Comment:* One comment indicated that there was not enough emphasis on transitional phrases and their impact on the adequacy of the written description. *Response:* As with the preamble, the transitional phrase is discussed in the context of the scope of the claimed invention as a whole.

(21) *Comment:* The Extension of Comment Period and Notice of Hearing requested comments as to how the transition terms "having" and "consisting essentially of" should be treated within the context of nucleotide and amino acid sequence claims. Two comments observed that transitional phrases in the context of nucleotide and amino acid sequence claims should have the same treatment as in chemical cases. Another comment stated that "consisting essentially of" language in DNA or vector claims should not be rejected as *per se* improper under 35 U.S.C. 112, ¶ 2. Two comments stated that lacking an art-accepted meaning or a definition in the specification, "having" would imply an open claim format; another comment stated that "having" is understood to mean "comprising." The term "consisting essentially of" was defined by one comment as a closed claim format that is essentially limited to the compound or composition defined explicitly following the transitional phrase, and by two other comments as having the stated sequence and excluding any alterations which materially change the structure and/or function of the specified sequence. One comment opined that "A DNA consisting essentially of SEQ ID NO: 1" would be limited to DNAs having the nucleotide sequence set forth in SEQ ID NO: 1 plus minor additions at the 5'— and/or 3' —ends of the recited sequence. Another comment observed that the meaning of "consisting essentially of" depends on how the specification defines its usage. *Response:* During examination, the claim as a whole is given the broadest reasonable interpretation consistent with the specification. Transitional phrases should be given the same treatment in all cases. The Revised Interim Guidelines set forth legally recognized definitions for transition language in an endnote. "Consisting essentially of" is acceptable transition language in nucleic acid and protein claims. The impact of the transition language on enablement and practical utility will not be dealt with in this forum.

(22) *Comment:* One comment criticized the use of the taxonomic terms "genus" and "species." The comment explained that because the terminology is well established in biology, it should not be applied to chemical compounds. Two comments described the Guidelines as deficient in analyzing the proper relationship of preamble, transitional phrase and claim body for distinguishing genus from species claims. According to another comment, the Guidelines confuse genus and species claims. *Response:* The Revised Interim Guidelines refer to the terms "genus" and "species" in their well accepted legal sense as widely used patent terms of art that are recognized as distinct from their use as taxonomic terms. The revision clarifies what is meant by genus and species.

(23) *Comment:* Several comments found the explanations for the examples deficient because they do not clarify what would constitute a sufficient disclosure. One comment urged that there is no guidance provided as to what would constitute sufficient identifying characteristics, and the Guidelines do not set forth the number of the examples needed for sufficient written description. Another comment urged that structure, or function plus partial structure, or function plus "some characteristics" (*e.g.*, 2 or more), is sufficient to meet the written description requirement. Yet another comment urged that uncertainties and potential problems exist because it is unclear how "relevant" or "sufficient" identifying characteristics are established; that it is unclear how functional properties fit into the analysis; and that problems exist with the level of uncertainty when the complete structure is not disclosed or the structure is not disclosed and only a few identifying characteristics are disclosed. Another comment urged that the methodology is incomplete as to how many identifying characteristics are required and what characteristics are relevant for description of a species. This comment applied the same reasoning to the number of species required for describing a genus. One comment urged that functional characteristics in combination with certain objectively defined physical characteristics can serve to characterize the compound sufficiently to establish possession, even in less developed arts. One comment urged that the ability to predict structure from function is given as a standard for the written description requirement without any citation to authority. *Response:* The Revised Interim Guidelines do not include examples within the text. The test for whether sufficient identifying characteristics have been disclosed is not a bright-line test, but rather requires weighing various factors including the level of skill and knowledge in the art, and the extent to which relevant identifying characteristics are described. The revision provides more guidance to the examiners by citing as examples cases involving mature arts with a high level of skill and knowledge (*e.g.*, *Pfaff* v. *Wells Electronics, Fonar Corp.* v. *General Electric Co.*, 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997) and *Vas-Cath* v. *Mahurkar*), as well as cases in emerging technologies where more description is necessary (*e.g.*, *Eli Lilly*, *Amgen* v. *Chugai*, and *Fiers* v. *Revel*). The test remains whether one of skill in the art, provided with the disclosure, would recognize that the applicant was in possession of the claimed subject matter when the application was filed.

(24) *Comment:* The Extension of Comment Period and Notice of Hearing requested comments on how the final Guidelines should address the deposit of a biological material made under 37 CFR 1.801, and comments on the extent to which a deposit of biological material may be relied upon to support the addition or correction of sequence information. Several comments expressed the opinion that deposit of a compound or biological material can be one means of demonstrating possession of a specifically claimed compound that has not otherwise been described in a complete manner in the specification. One comment stated that if a gene were cloned but not sequenced, and the vector in question were deposited, the sequence is an inherent property of the deposited vector and hence the description requirement would be satisfied if the claim referred to the deposit. One comment urged that the description requirement may be satisfied by the inherent properties of a disclosed structure, citing *Kennecott Corp.* v. *Kyocera Int'l Inc.*, 835 F.2d 1419, 5 USPQ2d 1194 (Fed. Cir. 1987). As for the later addition or correction of information, several comments indicated that actual possession established through a deposit with a partial characterization (*i.e.*, to correlate the physical description to the material that has been deposited, such as molecular weight, partial sequence) should be sufficient to avoid problems with new matter where the information added to a disclosure is an inherent characteristic of the compound or composition. One comment indicated that correcting a sequence based on more accurate sequencing of deposited material does not introduce new matter. One comment stated that present genus-species concepts should prevent an applicant from obtaining an unfair advantage by depositing a large amount of material and then relying on inherency; if a variety of materials are deposited in a single host, the specification must adequately describe how to isolate the intended molecule(s). Two comments expressly stated "no comment" with regard to the issue of adding a substantial amount of sequence information. One comment opined that the date of deposit is not controlling with regard to the issue of whether the written description requirement is met, and a second comment observed that *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985), cannot be limited by rule. *Response:* The Revised Interim Guidelines indicate that a deposit of a claimed biological material in accordance with the requirements of 37 CFR 1.801 *et seq.* is evidence of actual reduction to practice of the biological material. However, a deposit is not a substitute for a written description of the claimed invention. The Revised Interim Guidelines also address the issue of when a deposit can be relied upon to correct minor sequencing errors. However, addition of sequence information based on a deposit is not specifically addressed; these circumstances create issues yet to be resolved by the courts, and will be resolved on a case-by-case basis in the PTO. *See, e.g., In re Fisher*, 427 F.2d 833, 836, 166 USPQ 18, 21 (CCPA 1970).

(25) *Comment:* One comment explained that associating taxonomic groupings with gene sequences is a dated concept because genes are not distinguishable as to origin. The generic term "mammal gene" was said to be meaningless, absent an implied process limitation that the gene was obtained from a mammal. *Response:* The examples have been removed from the revision. However, the training materials will permit applicants to use taxonomic modifiers such as "mammalian" because the usage is ubiquitous in the literature and in patents and generally has an accepted meaning in the art.

(26) *Comment:* One comment urged that broad functional claims lacking defining structure should not be granted on the basis of a "not easily generalizable disclosure." A different comment stated that functional characteristics can be appropriate in all arts. Comments differed on hybridization, where some held it is a proper defining characteristic, and another stated it is insufficient. *Response:* The Revised Interim Guidelines do not establish per se rules regarding functional language. When used appropriately, functional language may provide an adequate written description of the claims invention as discussed in the Revised Interim Guidelines.

(27) *Comment:* Several comments indicated that the Guidelines present inadequate guidance with respect to analyzing written description support for genus claims. One comment stated that the Guidelines provide inadequate criteria for selection of appropriate genuses. Another comment stated that the Guidelines do not provide adequate guidance to determine whether an applicant has presented a properly formed genus, and suggested that "a genus designation should be strictly tied to the disclosed properties of the structures being claimed." Another comment stated that the Guidelines should clarify that the genus/species distinction is determined by the transitional phrase and body of the claim, not the preamble. Another comment stated that the Guidelines provide inadequate guidance as to the number of species required to meet the written description requirement for a genus. One comment urged that a relevant factor to consider is whether the claims cover embodiments broader than the essential elements of the embodiments described in the specification as in *Gentry Gallery Inc.* v. *Berkline*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998). According to this comment, species rarely, if ever, constitute sufficient support for generic claims unless accompanied by a general disclosure that is commensurate in scope with the claims. *Response:* The Revised Interim Guidelines follow Federal Circuit case law which requires a representative number of species to satisfy the written description requirement for a genus. Written description is a question of fact, and what constitutes a representative number for a genus is a factual determination left to a case-by-case analysis by the examiner.

(28) *Comment:* One comment urged that general allegations of "unpredictability in the art" are insufficient to support a case against the applicant, and that examiners should be instructed to weigh applicant's evidence of what the description provides to one of skill in the art. *Response:* The suggestion to clarify that a general allegation of "unpredictability in the art" is insufficient to support a rejection has been adopted. A disclosure as filed is *prima facie* adequate. To support a rejection, the PTO has the burden of showing why the applicant's evidence is insufficient. In any case where lack of written description is found, the PTO should cite documentary evidence in support of the finding. Where documentary evidence is not available, technical reasoning, as distinguished from legal reasoning, may support the finding when the technical line of reasoning relates to fact finding regarding possession of the invention.

(29) *Comment:* One comment indicated that rejections based on the enablement and written description requirements of 35 U.S.C. 112 should be made separately, and the rejections should not mix standards. *Response:* Examiners are directed to make separate rejections based on the enablement and written description requirements of 35 U.S.C. 112. *See, e.g.*, MPEP § 706.03(c) (explaining when it is appropriate to use a particular form paragraph for rejecting claims under 35 U.S.C. 112, ¶1) and MPEP § 2164 ("limitations must be

analyzed for both enablement and description using their separate and distinct criteria").

(30) *Comment*: One comment observed that the Guidelines do not guide examiners in how to suggest amendments to bring the claims into compliance. The comment also observed that examiners may be ill-equipped to deal with evaluating the sufficiency of applicant's efforts. *Response:* The training materials will provide guidance as to how rejections for lack of an adequate written description can be overcome.

(31) *Comment*: One comment stated that the Guidelines should instruct examiners to pay due regard to the scientific and commercial realities of each individual invention, such that the scope of the claims is a fair reflection of the applicant's contribution to the art. *Response*: The scientific and commercial realities of each invention are considered to the extent that they impact analysis of a claimed invention for compliance with Title 35 of the U.S. Code. The Office is bound to follow the law and cannot make judgment calls as to what is "a fair reflection of the applicant's contribution to the art."

(32) *Comment:* While two comments observed that the Guidelines should not have a significant impact on patents or pending or newly filed applications because they are only Guidelines which are not binding on the Board or examiners, three comments were of the opinion that the Guidelines would impact pending and newly filed cases by limiting the scope of patent protection. One comment was of the opinion that the Guidelines should have no impact on issued cases except reissues, whereas another expected many issued patents to be declared invalid (more as a result of *Eli Lilly* than the Guidelines). Another comment observed that the Guidelines should not impose significant new burdens on patent applicants in the biotechnology arts or give rise to a new "anti-patenting" posture in the biotechnology examination group; however, the PTO should not be misled into adapting "customer-friendly" examination standards that do not subject applications to a thorough and rigorous examination. One comment opined that the Guidelines will result in a great increase in the number of appeals until the Federal Circuit makes clear that the law is quite different, thus delaying commercialization of potentially life improving and life saving inventions. According to this comment, universities and small inventors do not have the financial support to provide the exhaustive kind of work the Guidelines can require for meaningful coverage; this will mean that many biotechnology inventions will not be commercialized. One comment stated that the Commissioner indicates that meaningful patent coverage is required for commercial exploitation of biotechnological inventions, yet the PTO continues to take a position that leads away from what the Commissioner espouses. Another comment felt that the scope of allowed claims would be dependent on the examiner; a potential applicant would not know what sort of claims could be obtained based on a particular disclosure. One comment opined that applications filed after publication of the Guidelines will probably be much more detailed and longer in length. *Response*: The Revised Interim Guidelines clarify that a written description issue should rarely arise for an original claim because such a claim is presumed to have adequate descriptive support. The burden is on the examiner to provide evidence or reasoning in support of any rejection. Such an approach would not be expected to increase the number of appeals, nor should it require exhaustive work for meaningful coverage. The Revised Interim Guidelines are intended to promote uniformity, not diminish it.

(33) *Comment*: One comment indicated it is premature to instruct examiners in the proposed Guidelines since they may change dramatically as a result of public comment. Three comments stated that the Guidelines should not be applied until final Guidelines have been approved; two of these indicated that the Guidelines should only be applied to applications filed after implementation. One comment suggested preparing separate guidance for currently pending applications. *Response*: Separate guidance is not required for pending applications and applications filed after implementation of any final Guidelines; the Guidelines do not establish new law or rules or impose any additional requirements on applicants.

(34) *Comment*: One comment requested that the PTO address the issue of open-claim language for EST claims in the final Guidelines because of their importance to the biotechnology industry. Several comments stated that permitting open-ended language with respect to an EST claim contradicts the written description requirement because the common structural features of the EST do not constitute a "substantial portion of the genus" as required by the *Eli Lilly* case. According to these commentators, a claim such as "a DNA comprising SEQ. ID. NO: 1" would lack written description when SEQ. ID. NO: 1 was a gene fragment. *Response*: The Revised Interim Guidelines maintain the view that use of such terms as "gene" in the preamble of an EST claim may raise a written description issue if one skilled in the art would understand that a "gene" requires elements which are not sufficiently described. However, claims to "a DNA comprising SEQ. ID. NO: 1" are unlikely to raise a written description issue. The comments do not explain why there is a written description problem for a claim such as "a DNA comprising SEQ. ID. 1" when SEQ. ID. 1 is an EST, while there is no problem when SEQ. ID. 1 is a whole gene or a gene promoter. The only difference seems to be the utility of the DNA fragment.

(35) *Comment*: One comment asserted that the scope and level of unpredictability of the structure is so large that the person skilled in the art could not envisage sufficient species to place the genus in possession of the inventor at the time of filing, and that it should be a rare disclosure that supports EST claims broader than the specific SEQ. ID, even for claims such as "a DNA comprising the EST of SEQ. ID. NO: 1." The comment also suggested that claim language that supports the introduction of an infinite amount of random sequence would require an immense number of exemplary species. Several commentators advanced the position that disclosure of only a small fragment does not convey that the inventor was in possession of all of the possible molecules or that the inventor was in possession of the fragment wherever it occurs. *Response*: A claim such as "a DNA comprising the EST of SEQ. ID. NO: 1" or "a gene comprising the EST of SEQ. ID. NO: 1" will be analyzed for compliance with the written description requirement by determining whether the partial structure in combination with any other disclosed relevant identifying characteristics are sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention as a whole. The Office does not agree with the comment that the scope of such an EST claim is necessarily too large to satisfy the written description requirement. The PTO has issued numerous patents in the past directed to nucleic acids that use open-ended language. Although an applicant presenting an original claim to an EST using open-ended claim language with disclosure of only the EST sequence is not in possession of any arbitrary specific possible molecule that contains the EST, the applicant may

be in possession of a broad genus of DNA where the EST is in any random nucleic acid sequence. The comment's statement to the contrary would preclude open-ended claims incorporating any DNA sequence such as gene or promoter. In fact, such a view would appear to preclude open-ended language for any other polymer. However, such open-ended EST claims may not comply with the utility and scope of enablement requirements of 35 U.S.C. 101 and 112.

**Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description" Requirement**

These revised interim "Written Description Guidelines" are intended to assist Office personnel in the examination of patent applications for compliance with the written description requirement of 35 U.S.C. 112, ¶ 1. This revision is based on the Office's current understanding of the law and public comments received in response to the PTO's previous request for public comments on its Interim Written Description Guidelines and is believed to be fully consistent with binding precedent of the U.S. Supreme Court, as well as the U.S. Court of Appeals for the Federal Circuit and its predecessor courts.

This revision does not constitute substantive rulemaking and hence does not have the force and effect of law. It is designed to assist Office personnel in analyzing claimed subject matter for compliance with substantive law. Rejections will be based upon the substantive law, and it is these rejections which are appealable. Consequently, any perceived failure by Office personnel to follow the Revised Interim Guidelines is neither appealable nor petitionable.

These Revised Interim Guidelines are intended to form part of the normal examination process. Thus, where Office personnel establish a *prima facie* case of lack of written description for a claim, a thorough review of the prior art and examination on the merits for compliance with the other statutory requirements, including those of 35 U.S.C. 101, 102, 103, and 112, is to be conducted prior to completing an Office action which includes a rejection for lack of written description. Office personnel are to rely on this revision of the guidelines in the event of any inconsistent treatment of issues involving the written description requirement between these Revised Interim Guidelines and any earlier guidance provided from the Office.

**I. General Principles Governing Compliance With the "Written Description" Requirement for Applications**

The first paragraph of 35 U.S.C. 112 requires that the "specification shall contain a written description of the invention. * * *" This requirement is separate and distinct from the enablement requirement.[1] The written description requirement has several policy objectives. "[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed."[2] Another objective is to put the public in possession of what the applicant claims as the invention. The written description requirement of the Patent Act promotes the progress of the useful arts by ensuring that patentees adequately describe their inventions in their patent specifications in exchange for the right to exclude others from practicing the invention for the duration of the patent's term.[3]

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.[4] An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations.[5] Possession may be shown by actual reduction to practice,[6] or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or other descriptions of the invention that are sufficiently specific to enable a person skilled in the art to practice the invention.[7] A question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently, a new or amended claim wherein a claim limitation has been added or removed, or a claim to entitlement of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c).[8] Compliance with the written description requirement is a question of fact which must be resolved on a case-by-case basis.[9]

*A. Original Claims*

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed.[10] However, the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.[11] The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art.[12] This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art recognized correlation or relationship between the structure of the invention and its function.[13] A lack of adequate written description problem also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.[14]

*B. New or Amended Claims*

The proscription against the introduction of new matter in a patent application[15] serves to prevent an applicant from adding information that goes beyond the subject matter originally filed.[16] Thus, the written description requirement prevents an applicant from claiming subject matter that was not adequately described in the specification as filed. New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement.[17] While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also the appropriate correction.[18]

Under certain circumstances, omission of a limitation can raise an issue regarding whether the inventor had possession of a broader, more generic invention.[19] A claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement.[20]

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.[21]

[1] See Endnotes at end of this notice.

## II. Methodology for Determining Adequacy of Written Description

### *A. Read and Analyze the Specification for Compliance With 35 U.S.C. 112, ¶ 1*

Office personnel should adhere to the following procedures when reviewing patent applications for compliance with the written description requirement of 35 U.S.C. 112, ¶ 1. The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed;[22] however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims.[23] Consequently, rejection of an original claim for lack of written description should be rare. The inquiry into whether the description requirement is met is a question of fact that must be determined on a case-by-case basis.[24]

#### 1. For Each Claim, Determine What the Claim as a Whole Covers

Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description.[25] The entire claim must be considered, including the preamble language[26] and the transitional phrase.[27] The claim as a whole, including all limitations found in the preamble,[28] the transitional phrase, and the body of the claim, must be sufficiently described in the specification to satisfy the written description requirement.[29]

The examiner should evaluate each claim to determine if sufficient structures, acts, or functions are recited to make clear the scope and meaning of the claim, including the weight to be given the preamble.[30] The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, ¶ 1, for lack of adequate written description. Limitations may not, however, be imported into the claims from the specification.

#### 2. Review the Entire Application to Understand What Applicant Has Described as the Essential Features of the Invention

Prior to determining whether the disclosure satisfies the written description requirement for the claimed subject matter, the examiner should review the claims and the entire specification, including the specific embodiments, figures, and sequence listings, to understand what applicant has identified as the essential distinguishing characteristics of the invention. The analysis of whether the specification complies with the written description requirement requires the examiner to determine the correspondence between what applicant has described as the essential identifying characteristic features of the invention, *i.e.*, what the applicant has demonstrated possession of, and what applicant has claimed. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed,[31] and should include a determination of the field of the invention and the level of skill and knowledge in the art. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art does not have to be described in detail in the specification.[32]

#### 3. Determine Whether There is Sufficient Written Description To Inform a Skilled Artisan That Applicant Was in Possession of the Claimed Invention as a Whole at the Time the Application Was Filed

a. Original claims.—Possession may be shown in any number of ways. Possession may be shown by actual reduction to practice, by a clear depiction of the invention in detailed drawings which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention, or by a written description of the invention describing sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention.[33]

A specification may show actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim, and determined that the invention would work for its intended purpose.[34] Actual reduction to practice of a biological material may be shown by specifically describing a deposit made in accordance with the requirements of 37 C.F.R. § 1.801 *et seq.*[35]

An applicant may show possession of an invention by disclosure of drawings that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole.[36] The description need only describe in detail that which is new or not conventional.[37] This is equally true whether the claimed invention is directed to a product or a process. Normally a reduction to drawings will adequately describe the claimed invention.[38]

An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention,[39] *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[40] What is conventional or well known to one skilled in the art need not be disclosed in detail.[41] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[42]

(1) For each claim drawn to a single embodiment or species:[43]

(a) Determine whether the application describes an actual reduction to practice of the claimed invention.

(b) If the application does not describe an actual reduction to practice, determine whether the invention is complete as evidenced by a reduction to drawings.

(c) If the application does not describe an actual reduction to practice or reduction to drawings, determine whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention.

(i) Determine whether the application as filed describes the complete structure (or acts of a process) of the claimed invention as a whole. The complete structure of a species or embodiment typically satisfies the requirement that the description be set forth "in such full, clear, concise, and exact terms" to show possession of the claimed invention.[44] If a complete structure is disclosed, the written description requirement is satisfied for that species or embodiment, and a rejection under 35 U.S.C. 112, ¶ 1 for lack of written description must not be made.

(ii) If the application as filed does not disclose the complete structure (or acts of a process) of the claimed invention as a whole, determine whether the specification discloses other relevant identifying characteristics sufficient to

describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention.[45] Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention.[46] In contrast, in emerging and unpredictable technologies, more evidence is required to show possession. For example, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim other than a product-by-process claim.[47] Furthermore, disclosure of partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention.[48]

Any claim to a species that does not meet the test described under at least one of (a), (b), or (c) must be rejected as lacking adequate written description under 35 U.S.C. 112, ¶ 1.

(2) For each claim drawn to a genus:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction practice (see (1)(a), above), reduction to drawings (see (1)(b), above), or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).[49]

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus.[50] Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.[51] If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, ¶ 1.

b. New claims, amended claims, or claims asserting entitlement to the benefit of an earlier priority date or filing date under 35 U.S.C. §§ 119, 120, or 365(c).—The examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims.[52] However, when filing an amendment an applicant should show support in the original disclosure for new or amended claims.[53] To comply with the written description requirement of 35 U.S.C. 112, ¶ 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly,[54] implicitly,[55] or inherently[56] supported in the originally filed disclosure.[57] Furthermore, each claim must include all elements which applicant has described as essential.[58]

If the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, ¶ 1, as lacking adequate written description, or in the case of a claim for priority under 35 U.S.C. 119, 120, or 365(c), the claim for priority must be denied.

## III. Complete Patentability Determination Under All Statutory Requirements and Clearly Communicate Findings, Conclusions and Their Bases

The above only describes how to determine whether the written description requirement of 35 U.S.C. 112, ¶ 1 is satisfied. Regardless of the outcome of that determination, Office personnel must complete the patentability determination under all the relevant statutory provisions of Title 35 of the U.S. Code.

Once Office personnel have concluded analysis of the claimed invention under all the statutory provisions, including 35 U.S.C. 101, 112, 102, and 103, they should review all the proposed rejections and their bases to confirm their correctness. Only then should any rejection be imposed in an Office action. The Office action should clearly communicate the findings, conclusions, and reasons which support them. When possible, the Office action should offer helpful suggestions on how to overcome rejections.

### *A. For Each Claim Lacking Written Description Support, Reject the Claim Under Section 112, ¶1, for Lack of Adequate Written Description*

A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption.[59] The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims.[60] In rejecting a claim, the examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:

(1) identify the claim limitation at issue; and

(2) establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability

in the art" is not a sufficient reason to support a rejection for lack of adequate written description.

When appropriate, suggest amendments to the claims which can be supported by the application's written description, being mindful of the prohibition against the addition of new matter in the claims or description.[61]

*B. Upon Reply By Applicant, Again Determine the Patentability of the Claimed Invention, Including Whether the Written Description Requirement is Satisfied by Reperforming the Analysis Described Above in View of the Whole Record*

Upon reply by applicant, before repeating any rejection under 35 U.S.C. 112, ¶ 1 for lack of written description, review the basis for the rejection in view of the record as a whole, including amendments, arguments, and any evidence submitted by applicant. If the whole record now demonstrates that the written description requirement is satisfied, do *not* repeat the rejection in the next Office action. If the record still does not demonstrate that written description is adequate to support the claim(s), repeat the rejection under 35 U.S.C. 112, ¶ 1, fully respond to applicant's rebuttal arguments, and properly treat any further showings submitted by applicant in the reply. Any affidavits, including those relevant to the 112, ¶ 1, written description requirement,[62] must be thoroughly analyzed and discussed in the next Office action.

ENDNOTES

1. *See, e.g., Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991).

2. *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977).

3. *See Regents of the University of California* v. *Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

4. *See, e.g., Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. Much of the written description case law addresses whether the specification as originally filed supports claims not originally in the application. The issue raised in the cases is most often phrased as whether the original application provides "adequate support" for the claims at issue or whether the material added to the specification incorporates "new matter" in violation of 35 U.S.C. § 132. The "written description" question similarly arises in the interference context, where the issue is whether the specification of one party to the interference can support the newly added claims corresponding to the count at issue, *i.e.*, whether that party can "make the claim" corresponding to the interference count. *E.g., see Martin* v. *Mayer*, 823 F.2d 500, 502, 3 USPQ2d 1333, 1335 (Fed. Cir. 1987).

In addition, early opinions suggest the Patent and Trademark Office was unwilling to find written descriptive support when the only description was found in the claims; however, this viewpoint was rejected. *See In re Koller*, 613 F.2d 819, 204 USPQ 702 (CCPA 1980) (original claims constitute their own description); *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973) (accord); *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) (accord). It is now well accepted that a satisfactory description may be in the claims or any other portion of the originally filed specification.

These early opinions did not address the quality or specificity of particularity that was required in the description, *i.e.*, how much description is enough.

5. *Lockwood* v. *American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

6. An application specification may show actual reduction to practice by describing testing of the claimed invention or, in the case of biological materials, by specifically describing a deposit made in accordance with 37 CFR 1.801 *et seq.* 37 CFR 1.804, 1.809. *See also Deposit of Biological Materials for Patent Purposes, Final Rule*, 54 FR 34,864 (August 22, 1989) ("The requirement for a specific identification is consistent with the description requirement of the first paragraph of 35 U.S.C. 112, and to provide an antecedent basis for the biological material which either has been or will be deposited before the patent is granted." *Id.* at 34876. "[T]he description must be sufficient to permit verification that the deposited biological material is in fact that disclosed. Once the patent issues, the description must be sufficient to aid in the resolution of questions of infringement." *Id.* at 34,880.). Such a deposit is not a substitute for a written description of the claimed invention. The written description of the deposited material needs to be as complete as possible because the examination for patentability proceeds solely on the basis of the written description. *See, e.g., In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985). *See also* 54 FR at 34,880 ("As a general rule, the more information that is provided about a particular deposited biological material, the better the examiner will be able to compare the identity and characteristics of the deposited biological material with the prior art.").

7. *Pfaff* v. *Wells Electronics, Inc.*, 525 U.S. 55,___, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998).

8. A description requirement issue can arise for original claims (*see, e.g., Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398) as well as new or amended claims. Most typically, the issue will arise in the context of determining whether new or amended claims are supported by the description of the invention in the application as filed (*see, e.g., In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989)), whether a claimed invention is entitled to the benefit of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c) (*see, e.g., Tronzo* v. *Biomet, Inc.*, 156 F.3d 1154, 47 USPQ2d 1829 (Fed. Cir. 1998); *Fiers* v. *Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993); *In re Ziegler*, 992 F.2d 1197, 1200, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993)), or whether a specification provides support for a claim corresponding to a count in an interference (*see, e.g., Fields* v. *Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970)).

9. *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

10. *In re Wertheim*, 541 F.2d at 262, 191 USPQ at 96.

11. See endnote 4.

12. For example, consider the claim "A gene comprising SEQ ID NO: 1." A determination of what the claim as a whole covers may result in a conclusion that specific structures such as a promoter, a coding region, or other elements are included. Although all genes encompassed by this claim share the characteristic of comprising SEQ ID NO: 1, there may be insufficient description of those specific structures (*e.g.*, promoters, enhancers, coding regions, and other regulatory elements) which are also included.

13. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. *Cf. In re Bell*, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) (holding that a process could not render the product of that process obvious under 35 U.S.C. 103). The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. *Eli Lilly*, 119 F.3d at 1567, 43 USPQ2d at 1405. The fact that a great deal more than just a process is necessary to render a product invention obvious means that a great deal more than just a process is necessary to provide written description for a product invention.

*Compare Fonar Corp.* v. *General Electric Co.*, 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997) ("As a general rule, where software constitutes part of a best mode of carrying out an invention, description of such a best mode is satisfied by a disclosure of the functions of the software. This is because, normally, writing code for such software is within the skill of the art, not requiring undue experimentation, once its functions have been disclosed * * *. Thus, flow charts or source code listings are not a requirement for adequately disclosing the functions of software.").

14. *See, e.g., Fujikawa* v. *Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably

lead" those skilled in the art to any particular species); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 122–23 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.").

15. 35 U.S.C. 132 and 251. *See also In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981). *See* Manual of Patent Examining Procedure (MPEP) §§ 2163.06–2163.07 (7th Ed., July 1998) for a more detailed discussion of the written description requirement and its relationship to new matter.

16. The claims as filed in the original specification are part of the disclosure and therefore, if an application as originally filed contains a claim disclosing material not found in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. *In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985).

17. *See, e.g., In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads).

18. *In re Oda*, 443 F.2d 1200, 170 USPQ 260 (CCPA 1971). With respect to the correction of sequencing errors in applications disclosing nucleic acid and/or amino acid sequences, it is well know that sequencing errors are a common problem in molecular biology. *See, e.g.*, Richterich, Peter, "Estimation of Errors in 'Raw' DNA Sequences: A Validation Study," *Genome Research*, 8:251–259 (1998). If an application as filed includes sequence information and references a deposit of the sequenced material made in accordance with the requirements of 37 CFR 1.801 *et seq.*, corrections of minor errors in the sequence may be possible based on the argument that one of skill in the art would have resequenced the deposited material and would have immediately recognized the minor error. Deposits made after the filing date can only be relied upon to provide support for the correction of sequence information if applicant submits a statement in compliance with 37 CFR 1.804 stating that the biological material which is deposited is a biological material specifically defined in the application as filed.

19. *See, e.g., Gentry Gallery, Inc.* v. *Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) (claims to a section sofa comprising, *inter alia*, a console and a control means were held invalid for failing to satisfy the written description requirement where the claims were broadened by removing the location of the control means.); *Johnson Worldwide Associates Inc.* v. *Zebco Corp.*, 175 F.3d 985, 993, 50 USPQ2d 1607, 1613 (Fed. Cir. 1999) (In *Gentry Gallery*, the "court's determination that the patent disclosure did not support a broad meaning for the disputed claim terms was premised on clear statements in the written description that described the location of a claim element—the 'control means'—as 'the only possible location' and that variations were 'outside the stated purpose of the invention.' *Gentry Gallery*, 134 F.3d at 1479, 45 USPQ2d at 1503. *Gentry Gallery*, then, considers the situation where the patent's disclosure makes crystal clear that a particular (*i.e.*, narrow) understanding of a claim term is an 'essential element of [the inventor's] invention.'"); *Tronzo* v. *Biomet, Inc.*, 156 F.3d 1154, 1159, 47 USPQ2d 1829, 1833 (Fed. Cir. 1998) (claims to generic cup shape were not entitled to filing date of parent application which disclosed "conical cup" in view of the disclosure of the parent application stating the advantages and importance of the conical shape.).

20. *See Gentry Gallery*, 134 F.3d at 1480, 45 USPQ2d at 1503; *In re Sus*, 306 F.2d 494, 134 USPQ 301 (CCPA 1962) ("[O]ne skilled in this art would not be taught by the written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only certain aryl radicals and certain specifically substituted aryl radicals [*i.e.*, aryl azides] would be suitable for such purposes."). A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may also be subject to rejection under 35 U.S.C. § 112, ¶ 1 as not enabling, or under 35 U.S.C. 112, ¶ 2. *See In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976); and *In re Collier*, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). *See also Reiffin* v. *Microsoft Corp.*, 48 USPQ2d 1274, 1277 (N.D. Cal. 1998) and MPEP § 2172.01.

21. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563–64, 19 USPQ2d at 1117.

22. *Wertheim*, 541 F.2d at 262, 191 USPQ at 96.

23. *See* MPEP §§ 714.02 and 2163.06 ("Applicant should * * * specifically point out the support for any amendments made to the disclosure."); and MPEP § 2163.04 ("If applicant amends the claims and points out where and/or how the originally filed disclosure supports the amendment(s), and the examiner finds that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of the filing of the application, the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.").

24. *See In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ("Precisely how close [to the claimed invention] the description must come to comply with § 112 must be left to case-by-case development."); *In re Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (inquiry is primarily factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure).

25. *See, e.g., In re Morris*, 127 F.3d 1048, 1053–54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

26. "Preamble language" is that language in a claim appearing before the transitional phase, e.g., before "comprising," "consisting essentially of," or "consisting of."

27. The transitional term "comprising" (and other comparable terms, e.g., "containing," "including," and "having") is "open-ended—it covers the expressly recited subject matter, alone or in combination with unrecited subject matter. *See, e.g., Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves the "claim open for the inclusion of unspecified ingredients even in major amounts"), *quoted with approval in Moleculon Research Corp* v. *CBS, Inc.*, 793 F.2d 1261, 1271, 229 USPQ 805, 812 (Fed. Cir. 1986). "By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention. A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format." *PPG Industries* v. *Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353–54 (Fed. Cir. 1998). For search and examination purposes, absent a clear indication in the specification of what the basic and novel characteristics actually are, 'consisting essentially of' will be construed as equivalent to "comprising." *See, e.g., PPG*, 156 F.3d at 1355, 48 USPQ at 1355 ("PPG could have defined the scope of the phrase 'consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.").

28. *See Pac-Tec Inc.* v. *Amerace Corp.*, 903 F.2d 796, 801, 14 USPQ2d 1871, 1876 (Fed. Cir. 1990) (determining that preamble language that constitutes a structural limitation is actually part of the claimed invention).

29. An applicant shows possession of the claimed invention by describing the claimed invention with all of its essential novel elements. *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

30. *See, e.g., Bell Communications Research, Inc.* v. *Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995) ("[A] claim preamble has the import that the claim as a whole suggests for it."); *Corning Glass Works* v. *Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989) (The determination of whether preamble recitations are structural limitations can be resolved only on review of the entirety of the application "to gain an understanding of what the inventors actually invented and intended to encompass by the claim.").

31. *See, e.g., Wang Labs.* v. *Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993).

32. *See, e.g., Hybritech Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379–80, 231 USPQ 81, 90 (Fed. Cir. 1986).

33. *Pfaff* v. *Wells Electronics, Inc.*, 119 S.Ct. at 311, 48 USPQ2d at 1646 ("The word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.' It is true that reduction to practice ordinarily provides the best evidence that an invention is complete. But just because reduction to practice is sufficient evidence of completion, it does not follow that proof of reduction to practice is necessary in every case. Indeed, both the facts of the *Telephone Cases* and the facts of this case demonstrate that one can prove that an invention is complete and ready for patenting before it has actually been reduced to practice.").

34. *Cooper* v. *Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). *See also UMC Elecs. Co.* v. *United States*, 816 F.2d 647, 652, 2 USPQ2d 1465, 1468 (Fed. Cir. 1987) ("[T]here cannot be a reduction to practice of the invention * * * without a physical embodiment which includes all limitations of the claim."); *Estee Lauder Inc.* v. *L'Oreal S.A.*, 129 F.3d 588, 593, 44 USPQ2d 1610, 1614 (Fed. Cir. 1997) ("[A] reduction to practice does not occur until the inventor has determined that the invention will work for its intended purpose."); *Mahurkar* v. *C.R. Bard Inc.*, 79 F.3d 1572, 1578, 38 USPQ2d 1288, 1291 (Fed. Cir. 1996) (determining that the invention will work for its intended purpose may require testing depending on the character of the invention and the problem it solves).

35. 37 CFR §§ 1.804, 1.809. *See also* endnote 6.

36. *See, e.g., Vas-Cath*, 935 F.2d at 1565, 19 USPQ2d at 1118 ("drawings alone may provide a 'written description' of an invention as required by § 112"); *In re Wolfensperger*, 302 F.2d 950, 133 USPQ 537 (CCPA 1962) (the drawings of applicant's specification provided sufficient written descriptive support for the claim limitation at issue); *Autogiro Co. of America* v. *United States*, 384 F.2d 391, 398, 155 USPQ 697, 703 (Ct. Cl. 1967) ("[I]n those instances where a visual representation can flesh out words, drawings may be used in the same manner and with the same limitations as the specification.").

37. *See Hybritech* v. *Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94; *Fonar Corp.* v. *General Electric Co.*, 107 F.3d at 1549, 41 USPQ2d at 1805 (source code description not required).

38. This is especially true for the mechanical and electrical arts. *See, e.g., Pfaff* v. *Wells Electronics*, 119 S.Ct. at 312, 48 USPQ2d at 1647.

39. For example, the presence of a restriction enzyme map of a gene may be relevant to a statement that the gene has been isolated. One skilled in the art may be able to determine when the gene disclosed is the same as or different from a gene isolated by another by comparing the restriction enzyme map. In contrast, evidence that the gene could be digested with a nuclease would not normally represent a relevant characteristic since any gene would be digested with a nuclease. Similarly, isolation of an mRNA and its expression to produce the protein of interest is strong evidence of possession of an mRNA for the protein.

Examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. *See Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention").

However, a definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. *See also Fiers*, 984 F.2d at 1169–71, 25 USPQ2d at 1605–06 (discussing *Amgen Inc.* v. *Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)).

40. If a claim limitation invokes 35 U.S.C. § 112, ¶ 6, it must be interpreted to cover the corresponding structure, materials, or acts in the specification and "equivalents thereof." See 35 U.S.C. 112, ¶ 6. *See also B. Braun Medical, Inc.* v. *Abbott Lab.*, 124 F.3d 1419, 1424, 43 USPQ2d 1896, 1899 (Fed. Cir. 1997). If the written description fails to set forth the supporting structure, material or acts corresponding to the means-(or step-) plus-function, the claim may not meet the requirement of 35 U.S.C. 112, ¶ 1. A means-(or step-) plus-function claim limitation satisfies 35 U.S.C. 112, ¶ 1 if: (1) The written description links or associates particular structure, materials, or acts to the function recited in a means-(or step-) plus-function claim limitation; or (2) it is clear based on the facts of the application that one skilled in the art would have known what structure, materials, or acts perform the function recited in a means-(or step-) plus-function limitation. In considering whether there is 35 U.S.C. § 112, ¶ 1 support for the claim limitation, the examiner must consider not only the original disclosure contained in the summary and detailed description of the invention portions of the specification, but also the original claims, abstract, and drawings. See the Interim Supplemental Examination Guidelines for Determining the Applicability of 35 U.S.C. 112 ¶ 6, 64 FR 41392 (July 30, 1999).

41. *See Hybritech Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94.

42. *See, e.g., Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin* v. *Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

43. A claim which is limited to a single disclosed embodiment or species is analyzed as a claim drawn to a single embodiment or species, whereas a claim which encompasses two or more embodiments or species within the scope of the claim is analyzed as a claim drawn to a genus. *See also* MPEP § 806.04(e).

44. 35 U.S.C. 112, ¶ 1. *Cf. Fields* v. *Conover*, 443 F.2d 1386, 1392, 170 USPQ 276, 280 (CCPA 1971) (finding a lack of written description because the specification lacked the "full, clear, concise, and exact written description" which is necessary to support the claimed invention).

45. For example, if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession: it does not satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372–73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). *Compare Fonar*, 107 F.3d at 1549, 41 USPQ2d at 1805 (disclosure of software function adequate in that art).

46. *See, e.g., In re Hayes Microcomputer Products Inc. Patent Litigation*, 982 F.2d 1527, 1534–35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992) ("One skilled in the art would know how to program a microprocessor to perform the necessary steps described in the specification. Thus, an inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains. Disclosing a microprocessor capable of performing certain functions is sufficient to satisfy the requirement of section 112, first paragraph, when one skilled in the relevant art would understand what is intended and know how to carry it out.")

47. *See, e.g., Fiers* v. *Revel*, 984 F.2d at 1169, 25 USPQ2d at 1605; *Amgen Inc.* v. *Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). Where the process has actually been used to produce the product, the written description requirement for a product-by-process claim is clearly satisfied; however, the requirement may not be satisfied where it is not clear that the acts set forth in the specification can be performed, or that the product is produced by that process.

48. *See, e.g., Amgen Inc.* v. *Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206, 18

USPQ2d 1016, 1021 (Fed. Cir. 1991)("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.")(citations omitted). In such instances the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co.* v. *Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention. *Id.*

49. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

50. *See, e.g., Eli Lilly*.

51. For example, in the genetics arts, it is unnecessary for an applicant to provide enough different species that the disclosure will permit one of skill to determine the nucleic acid or amino acid sequence of another species from the application alone. The stochastic nature of gene evolution would make such a predictability nearly impossible. Thus, the Federal Circuit could not have intended that representative number requires predictability of sequences.

52. *See Wertheim*, 541 F.2d at 263, 191 USPQ at 97 ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."). *See also* MPEP § 2163.05.

53. *See* MPEP §§ 714.02 and 2163.06 ("Applicant should * * * specifically point out the support for any amendments made to the disclosure.").

54. *See, e.g., In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989)(Original specification for method of forming images using photosensitive microcapsules which describes removal of microcapsules from surface and warns that capsules not be disturbed prior to formation of image, unequivocally teaches absence of permanently fixed microcapsules and supports amended language of claims requiring that microcapsules be "not permanently fixed" to underlying surface, and therefore meets description requirement of 35 U.S.C. 112.).

55. *See, e.g., In re Robins*, 429 F.2d 452, 456–57, 166 USPQ 552, 555 (CCPA 1970) ("[W]here no explicit description of a generic invention is to be found in the specification * * * mention of representative compounds may provide an implicit description upon which to base generic claim language."); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972)(a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads).

56. *See, e.g., In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950–51 (Fed. Cir. 1999)("To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'") (citations omitted).

57. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation." *Hyatt* v. *Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998).

58. *See, e.g., Johnson Worldwide Associates Inc.* v. *Zebco Corp.*, 175 F.3d at 993, 50 USPQ2d at 1613; *Gentry Gallery, Inc.* v. *Berkline Corp.*, 134 F.3d at 1479, 45 USPQ2d at 1503; *Tronzo* v. *Biomet, Inc.*, 156 F.3d at 1159, 47 USPQ2d at 1833; and *Reiffin* v. *Microsoft Corp.*, 48 USPQ2d at 1277.

59. *See, e.g., In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

60. *Wertheim*, 541 F.2d at 262, 191 USPQ at 96.

61. *See In re Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326.

62. *See In re Alton*, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

Dated: December 16, 1999.

**Q. Todd Dickinson,**

*Assistant Secretary of Commerce and Commissioner of Patents and Trademarks.*

[FR Doc. 99–33053 Filed 12–20–99; 8:45 am]

BILLING CODE 3510–16–P

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## DEPARTMENT OF COMMERCE

## Patent and Trademark Office

**[Docket No. 991027289–9289–01]**

**RIN 0651–AB09**

## Revised Utility Examination Guidelines; Request for Comments

**AGENCY:** Patent and Trademark Office, Commerce.

**ACTION:** Notice and request for public comments.

**SUMMARY:** The Patent and Trademark Office (PTO) requests comments from any interested member of the public on the following Revised Utility Examination Guidelines. The PTO is publishing a revised version of guidelines to be used by Office personnel in their review of patent applications for compliance with the utility requirement based on comments received in response to the Request for Comments on Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement; Extension of Comment Period and Notice of Hearing, 63 FR 50837 (September 23, 1998). These Revised Utility Guidelines will be used by PTO personnel in their review of patent applications for compliance with the "utility" requirement of 35 U.S.C. 101. This revision supersedes the Utility Examination Guidelines that were published at 60 FR 36263 (1995) and at 1177 O.G. 146 (1995).

**DATES:** Written comments on the Revised Utility Examination Guidelines will be accepted by the PTO until March 22, 2000.

**ADDRESSES:** Written comments should be addressed to Box 8, Commissioner of Patents and Trademarks, Washington, DC 20231, marked to the attention of Mark Nagumo, or to Box Comments, Assistant Commissioner for Patents, Washington, DC 20231, marked to the attention of Linda S. Therkorn. Alternatively, comments may be submitted to Mark Nagumo via facsimile at (703) 305–9373 or by electronic mail addressed to "mark.nagumo@uspto.gov"; or to Linda Therkorn via facsimile at (703) 305–8825 or by electronic mail addressed to "linda.therkorn@uspto.gov."

**FOR FURTHER INFORMATION CONTACT:** Mark Nagumo by telephone at (703) 305–8666, by facsimile at (703) 305–9373, by electronic mail "mark.nagumo@uspto.gov," or by mail marked to his attention addressed to the Commissioner of Patents and Trademarks, Box 8, Washington, DC 20231; or Linda Therkorn by telephone at (703) 305–9323, by facsimile at (703) 305–8825, by electronic mail at "linda.therkorn@uspto.gov," or by mail marked to her attention addressed to Box Comments, Assistant Commissioner of Patents and Trademarks, Washington, DC 20231.

**SUPPLEMENTARY INFORMATION:** The PTO requests comments from any interested member of the public on the following Revised Utility Examination Guidelines. As of the publication date of this notice, this revision will be used by PTO personnel in their review of patent

# United States Patent [19]

**Rutter et al.**

[11] **Patent Number: 4,652,525**

[45] **Date of Patent: Mar. 24, 1987**


[54] **RECOMBINANT BACTERIAL PLASMIDS CONTAINING THE CODING SEQUENCES OF INSULIN GENES**


[75] Inventors: **William J. Rutter; Raymond Pictet; John Chirgwin; Howard M. Goodman; Axel Ullrich; John Shine,** all of San Francisco, Calif.

[73] Assignee: **The Regents of the University of California,** Berkeley, Calif.



[21] Appl. No.: **508,651**

[22] Filed: **Jun. 28, 1983**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 897,709, Apr. 19, 1978, abandoned, which is a continuation-in-part of Ser. No. 801,343, May 27, 1977, abandoned, and a continuation-in-part of Ser. No. 805,023, Jun. 9, 1977, abandoned.

[51] Int. Cl.[4] ..... C12N 1/20; C12N 1/00; C12N 15/00; C12R 1/19

[52] U.S. Cl. ..... **435/253**; 435/317; 435/172.3; 435/849

[58] Field of Search ..... 435/172.3, 68, 70, 71, 435/253, 317



[56] **References Cited**

U.S. PATENT DOCUMENTS

4,440,859 4/1984 Rutter et al. ..... 435/68

OTHER PUBLICATIONS

Wood et al, Nucleic Acids Research, vol. 3, pp. 1961–1971, Aug. 1976.

Higuchi et al, PNAS USA, vol. 73, pp. 3146–3150, Sep. 1976.

Rougeon et al, Nucleic Acids Research, vol. 2, pp. 2365–2378.

Chan et al, PNAS, vol. 73, pp. 1964–1968, Jun. 1976.



*Primary Examiner*—Alvin E. Tanenholtz

*Attorney, Agent, or Firm*—Ciotti & Murashige



[57] **ABSTRACT**

A recombinant procaryotic microorganism containing the gene coding for insulin.


**7 Claims, No Drawings**

clones was carried out on plates containing 20 μg/ml ampicillin.

## EXAMPLE 5

The DNA from pAU-1 as described in Example 4 was further purified by electrophoresis on a 6% polyacrylamide gel. After elution from the gel the DNA was labeled by incubation with $\gamma$-$^{32}$P-ATP and the enzyme polynucleotide kinase under conditions described by Maxam and Gilbert, supra. The enzyme catalyzes the transfer of a radiactive phosphate group from $\gamma$-$^{32}$P-ATP to the 5'-ends of the DNA. The enzyme was obtained from *E. coli* by the method of Panet, A., et al., *Biochemistry* 12, 5045 (1973). The DNA thus labeled was cleaved with Hae III endonuclease as described in Example 2, and the two labeled fragments, about 265 and 135 base pairs respectively, were separated on a polyacrylamide gel under the conditions described in Example 1. The isolated fragments were subjected to specific cleavage reactions and sequence analysis according to the method of Maxam and Gilbert, supra. The sequence below is based upon a composite of the findings from this series of experiments and those of a similar series of cDNA using plasmid vectors derived from col E1 such as pMB9 and pBR322. In the sequence of the 5' end, a sequence estimated between 50–120 nucleotides in length is undetermined and the poly dA segment at the 3'-end is of varying length. This sequence is provided as representing the best information presently available, with the understanding that ongoing studies may reveal additional details or may indicate a need for slight revision in some areas. The corresponding amino acid sequence of rat proinsulin I begins at the triplet position marked 1 and ends at triplet position marked 86. Some uncertainty remains with respect to the sequence underlined with a dashed line.

[undetermined] —GCC CTG CTC GTC CTC TGG GAG CCC AAG CCT GCT CAG GCT TTT GTC AAA CAG CAC CTT TGT
GGT CCT CAC CTG GTG GAG GCT CTG TAC CTG GTG TGT GGG GAA CGT GGT TTC TTC TAC ACA CCC AAC
TCC CGT CGT GAA GTG GAG GAC CCG CAA GTG CCA CAA CTG GAG CTG GCT GGA GGC CCG GAG GCC GGG
GAT CTT CAG ACC TGG GCA CTG GAG GTT GCC CGG CAG AAG CGT GGC ATT GTG GAT CAG TGC TGC ACC
AGC ATC TGC TCC CTC TAC CAA CTG CAG AAC TAC TGC AAC TGA
GTTCAATCAATTCCCGATCCACCCCTCTGCAATGAATAAAGCCTTTGAATGAGC-poly A
Scored Sections = Areas of Present Uncertainty

## EXAMPLE 6

A nucleotide sequence coding for human insulin is isolated, purified and incorporated in a plasmid essentially as described in Examples 1–4, starting from human pancreas tissue isolated from a suitable human source such as a donated pancreas or a fresh cadaver or a human insulinoma. A microorganism is produced, essentially as described in Example 4, having a nucleotide sequence coding for the human insulin A chain and B chain. The known amino acid sequence of human insulin A chain is:

Gly—Ile—Val—Glu—Gln—Cys—Cys—Thr—Ser—Ile—
—Cys—Ser—Leu—Tyr—Glu—Leu—Glu—Asn—
—Tyr—Cys—Asn

The known amino acid sequence of the human insulin B chain is:

Phe—Val—Asn—Glu—His—Leu—Cys—Gly—Ser—His—
—Leu—Val—Glu—Ala—Leu—Tyr—Leu—Val—Cys—Gly—
—Glu—Arg—Gly—Phe—Phe—Tyr—Thr—Pro—Lys—Thr

The amino acid sequences are numbered from the end having a free amino group. See Smith, L. F., *Diabetes* 21 (suppl. 2), 458 (1972).

## GENERAL CONCLUDING REMARKS

With the process of the present invention it has become possible for the first time to isolate a nucleotide sequence coding for a specific regulatory protein from a higher organism such as a vertebrate, and transfer the genetic information contained therein to a microorganism where it may be replicated indefinitely. The disclosed process may be applied to the isolation and purification of the human insulin gene, and to its transfer to a microorganism. A novel recombinant plasmid is disclosed, containing within its nucleotide sequence a subsequence having the structure of and transcribed from a gene of a higher organism. A novel microorganism is disclosed, modified to contain a nucleotide sequence having the structure of and transcribed from a gene of a higher organism. The practice of the invention has been illustrated by demonstrating the transfer of the rat gene for the proinsulin I to a strain of *Escherichia coli.* The sequence of the main portion of the transferred gene has been determined and has been found to contain the entire amino acid sequence of rat proinsulin I, as determined by reference to the known genetic code which is common to all forms of life.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains or which would be readily apparent to those skilled in said art. With that understanding, the invention is not to be limited except to the extent required by the appended claims.

What is claimed is:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

2. A recombinant procaryotic microorganism modified to contain a nucleotide sequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

3. The bacterium *Escherichia coli* which has been modified to contain a nucleotide sequence having the structure of and transcribed from the rat gene for insulin.

4. A microorganism according to claim 2 wherein the vertebrate is a mammal.

5. A microorganism according to claim 2 wherein the vertebrate is a human.

6. A plasmid according to claim 1 comprising a plasmid containing at least one genetic determinant of col E1.

7. A microorganism according to claim 2 comprising a strain of *Escherichia coli*.

* * * * *

# United States Patent [19]

**Bell et al.**

[11] **4,431,740**

[45] **Feb. 14, 1984**


[54] **DNA TRANSFER VECTOR AND TRANSFORMED MICROORGANISM CONTAINING HUMAN PROINSULIN AND PRE-PROINSULIN GENES**


[75] Inventors: **Graeme Bell; Raymond Pictet; Howard M. Goodman; William J. Rutter, all of San Francisco, Calif.**

[73] Assignee: **The Regents of the University of California, Berkeley, Calif.**



[21] Appl. No.: **386,338**

[22] Filed: **Jun. 8, 1982**

Related U.S. Application Data

[63] Continuation of Ser. No. 75,192, Sep. 12, 1979, abandoned.

[51] Int. Cl.³ ..... C12N 1/20; C12N 15/00; C12N 1/00; C12P 21/00

[52] U.S. Cl. ..... 435/253; 435/68; 435/172; 435/317

[58] Field of Search ..... 435/172, 253, 317



[56] References Cited

U.S. PATENT DOCUMENTS

4,237,224 12/1980 Cohen et al. ..... 435/172

OTHER PUBLICATIONS

Crea et al., PNAS, USA, vol. 75, pp. 5765-5769, Dec. 1978.
Villa-Komaroff et al., PNAS, vol. 75, pp. 3727-3731, Aug. 1978.
Ullrich et al, Science, vol. 196, pp. 1313-1319, Jun. 17, 1977.
Ullrich et al., Proceedings of the Symposium on Proinsulin, Insulin and C-Peptide, pp. 20-26, Jul. 1978.
Chang et al., Nature, vol. 275, pp. 617-624, Oct. 1978.
Martial et al., Science, vol. 205, pp. 602-606, Aug. 1979.
Mercereau-Puijalon, Nature, vol. 275, pp. 505-510, Oct. 1978.
Goeddel et al., Proc. Nat. Acad. Sci., USA, vol. 76, pp. 106-110, Jan. 1979.
Goeddel et al., Nature, vol. 281, pp. 544-550, Oct. 1979.
O'Farrell et al., J. of Bacteriology, vol. 134, pp. 645-654, May 1978.
Englund, The Journal of Biological Chemistry, vol. 246, pp. 3269-3276 (1971).
Kemmler et al., The Journal of Biological Chemistry, vol. 246, pp. 6786-6791 (1971).
Englund, J. Mol. Biol., vol. 66, pp. 209-224 (1972).
Polisky et al., PNAS, USA, vol. 73, pp. 3900-3904 (1976).



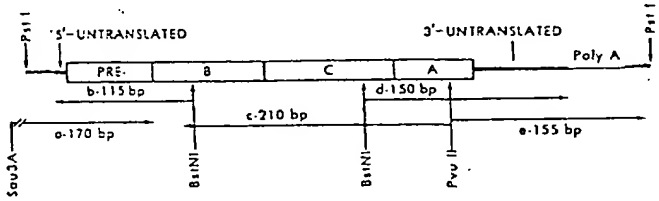
*Primary Examiner*—Alvin E. Tanenholtz
*Attorney, Agent, or Firm*—Keil & Witherspoon



[57] **ABSTRACT**

A DNA having a base sequence coding for human proinsulin and a DNA having a base sequence coding for human pre-proinsulin have been cloned, and novel recombinant DNA transfer vectors containing said cloned DNAs have been constructed. Novel microorganisms transformed by said recombinant transfer vectors have been obtained. Certain of said transformed microorganisms have demonstrated capability to express the cloned DNA's, synthesizing a protein comprising human proinsulin and a protein-comprising human pre-proinsulin.


**14 Claims, 2 Drawing Figures**



Alternatively, the fusion protein is treated with a combination of trypsin and carboxypeptidase B (or cathepsin B) to yield active insulin from the fusion protein in a single reaction.

C. A proinsulin coding sequence is constructed by selective cleavage at an internal site in the proinsulin coding region, followed by ligation of a chemically synthesized sequence coding for that part of the proinsulin coding region removed by the previous cleavage. The plasmid pcHI-1 is used as a source of the proinsulin coding region, which is selectively excised by treatment with Pst I endonuclease or preferably by treatment with Hha I endonuclease, as described in Example 2B.

Either fragment, after isolation is treated with alkaline phosphatase to remove the 5' terminal phosphate groups, then cleaved by treatment with a restriction endonuclease having a unique cleavage point in the proinsulin coding sequence. Preferably the restriction site is located near one of the ends of the proinsulin coding sequence. The Alu I site in region of amino acids 13-14 provides a convenient cleavage point (see FIG. 2). The Hha I fragment of pcHI-1 is partially cleaved with Alu I endonuclease to generate two fragments of approximately 76bp and approximately 375bp, respectively. The Alu I fragments are fractionated by gel electrophoresis, as described in Example 2A, and the 375bp fragment is recovered.

A nucleotide sequence coding for the first 13 amino acids of proinsulin with a 5'-terminal G (on the plus strand), to complete the codon for alanine at position 14, is synthesized by the phosphotriester method. Itakura, K., et al. J. Biol. Chem. 250, 4592 (1975) and Itakura, K., et al., J. AM. Chem. Soc. 97, 7327 (1975). The plus strand of the synthetic DNA has the sequence 5'-TTTGTGAACCAACACCTG TGCGGCTCACACCTGGTGGAAG-3', corresponding to the natural sequence. However, other sequences coding for the same amino acids may be synthesized. In general the sequence is 5'-TTKGTLAAK-CAJCAKXTYTGKGGLQRSCAKXTYGTLCAJG-3'. The resulting sequence is blunt-end ligated with the approximately 375bp fragment of the Hba I fragment of pcHI-1. Since the latter has a 5'-phosphate only at the end to be joined, the two fragments will be joined in the correct order. The synethetic fragment is correctly joined to the larger fragment in approximately 50% of the reactions.

The ligase-treated DNA is then cloned into a suitable expression plasmid, either by oligo-A tailing, as described in Example 2B, or by attachment or linkers and insertion into expression plasmids of known reading frames. In the case of oligo-A trailed inserts, expression of proinsulin is observed in about 1/12 of the clones. In the case of direct insertion where the reading frame is known to be correct, the frequency of expression clones is about 50%.

## EXAMPLE 3

Expression of human preproinsulin and proinsulin. The cloned inserts coding for preproinsulin (Example 1) or proinsulin (Example 2) are inserted in an expression transfer vector. When the insertion occurs in the correct orientation with respect to initiation of translation at the insertion site, and the insert is in reading frame phase with the promotor and ribosome binding site, the protein product of the cloned gene is synthesized by actively metabolizing host cells transformed by the transfer vector. The protein product is a fusion protein if the expression transfer vector contains a portion of a procaryotic gene between the promoter and the insertion site. However the insertion may be made immediately adjacent to a promoter site. In such cases, the protein coded by the insert is synthesized directly. Both techniques present advantages and disadvantages. Fusion proteins have the advantage that they tend to stabilize the foreign protein coded by the inserted gene. Also, desirable functional properties such as excretion from the host cell are conferred by fusion with certain host proteins such as $\beta$-lactamase. On the other hand, purification of the insert coded sequence is complicated by the general desirability of specifically removing the host portion of the fusion protein. Such removal is accomplished by known techniques as described in Examples 2A and 2B. Direct synthesis of the desired protein obviates the need for specific cleavage but generally precludes the possibility of excretion from the host cell.

Expression plasmids have been developed wherein expression is controlled by the lac promoter (Itakura, et al., Science 198, 1056 (1977), Ullrich, A., et al., Excerpta Medica, (1979); by the trp promoter (Martial, et al., Science 205, 602 (1979); and by the $\beta$-lactamase promoter, U.S. application Ser. No. 44,547, incorporated herein by reference.

Expression is detected by measurement of a product capable of binding immunochemically with anti-insulin antibody, or anti-proinsulin antibody. Radioimmunoassay, in which the antibody is radioactively labeled and antigen-antibody pairs are precipitated by a preparation of heat-killed Staphyloccoccus aureus C is employed. (See Morgan and Lazarow, Diabetes 12, 115 (1963) and Kessler, S. W., J. Immunol., 115, 1617 (1975). Radioimmune screening, as described by Erlich, H. A., et al., Cell 10, 681 (1978) or by Broome, S. and Gilbert, W., Proc. Nat. Acad. Sci. USA, 75, 2746 (1978), is used for detecting expression in bacterial colonies.

Fusion proteins indicative of expression are detected by comparing molecular weights of the host protein contributing the N-terminal part of the fusion protein, in host cells transformed by expression plasmids with and without an insert. A preferred variant is to employ the minicell-producing *E. coli* strain P678-54 as host. Radioactively labeled amino acids are incorporated into minicell proteins, comparing strains transformed with expression transfer vectors with and without the inserted proinsulin coding sequence. The proteins are fractionated by SDS-acrylamide gel electrophoresis and the protein positions detected by autoradiography. Expression of proinsulin is indicated by the presence of a labeled protein band found only in minicells transformed by the proinsulin expression plasmid. The position of the electrophoretic band provides a measure of the molecular weight of the expressed protein, and is consistent with the known length of the inserted gene and of the N-terminal procaryotic portion.

Removal of the procaryotic portion and conversion of proinsulin to insulin in vitro are carried out by known procedures, as described in detail supra.

What is claimed is:

1. A DNA transfer vector comprising an inserted cDNA consisting essentially of a deoxynucleotide sequence coding for human pre-proinsulin, the plus strand of said cDNA having a defined 5' end, said 5' end being the first deoxynucleotide of the sequence coding for said pre-proinsulin.

2. A DNA transfer vector comprising an inserted cDNA consisting essentially of a deoxynucleotide se-

quence coding for human proinsulin, the plus strand of said cDNA having a defined 5' end, said 5' end being the first deoxynucleotide of the sequence coding for said proinsulin.

3. A microorganisms transformed by the transfer vector of claim 1 or 2.

4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human pre-proinsulin consisting essentially of a plus strand having the sequence:

5'—$_{-24}$GCL$_{-23}$X$_{-22}$TY$_{-22}$TGG$_{-21}$ATG$_{-20}$W$_{-1}$-$_{9}$GZ$_{-19}$X$_{-18}$TY$_{-18}$X$_{-17}$TY$_{-17}$CCL$_{-16}$X$_{-15}$T-Y$_{-15}$X$_{-14}$TY$_{-14}$GCL$_{-13}$X$_{-12}$TY$_{-12}$X$_{-11}$TY$_{-11}$GCL$_{-10}$X$_{-9}$TY$_{-9}$TGG$_{-8}$GGL$_{-7}$CCL$_{-6}$GA-K$_{-5}$CCL$_{-4}$GCL$_{-3}$GCL$_{-2}$GCL$_{-1}$TTK$_{1}$GTL$_{2}$-AAK$_{3}$CAJ$_{4}$CAK$_{5}$X$_{6}$TY$_{6}$TGK$_{7}$GGL$_{8}$QR$_{9}$S$_{9}$CA-K$_{10}$X$_{11}$TY$_{11}$GTL$_{12}$GAJ$_{13}$GCL$_{14}$X$_{15}$TY$_{15}$TAK$_{16}$-X$_{17}$TY$_{17}$GTL$_{18}$TGK$_{19}$GCL$_{20}$GAJ$_{21}$W$_{22}$GZ$_{22}$G-CL$_{23}$TTK$_{24}$TTK$_{25}$TAK$_{26}$AC-L$_{27}$CCL$_{28}$AAJ$_{29}$ACL$_{30}$W$_{31}$GZ$_{31}$W$_{32}$GZ$_{32}$GAJ$_{3-3}$GCL$_{34}$GAJ$_{35}$GAK$_{36}$X$_{37}$TY$_{37}$CAJ$_{38}$GTL$_{39}$GG-L$_{40}$CAJ$_{41}$GTL$_{42}$GAJ$_{43}$X$_{44}$TY$_{44}$GGL$_{45}$GGL$_{46}$G-GL$_{47}$CCL$_{43}$GGL$_{49}$GCL$_{50}$GGL$_{51}$QR$_{52}$S$_{52}$X$_{53}$TY-$_{53}$CAJ$_{54}$CCL$_{55}$X$_{56}$TY$_{56}$GCL$_{57}$X$_{58}$TY$_{58}$GAJ$_{59}$G-GL$_{60}$QR$_{61}$S$_{61}$X$_{62}$TY$_{62}$CAJ$_{63}$AAJ$_{64}$W$_{65}$GZ$_{65}$GG-L$_{66}$ATM$_{67}$GTL$_{68}$GAJ$_{69}$CAJ$_{70}$TGK$_{71}$TGK$_{72}$A-CL$_{73}$QR$_{74}$S$_{74}$ATM$_{75}$TGK$_{76}$QR$_{77}$S$_{77}$X$_{78}$TY$_{78}$T-AK$_{79}$CAJ$_{80}$X$_{81}$TY$_{81}$GAJ$_{32}$AAK$_{83}$TAK$_{84}$TGK-$_{85}$AAK$_{86}$TAGACGCAGCCCGCAGG-CAGCCCCCCACCCGCCGCCTCCTGCACC-GAGAGAGATGGAATAAAGCCCTTGAAC-CAGC poly A-3' wherein

A is deoxyadenyl,
G is deoxyguanyl,
C is deoxycytosyl,
T is thymidyl,
J is A or G;
K is T or C;
L is A, T, C, or G;
M is A, C or T;
$X_n$ is T or C if $Y_n$ is A or G; and C if $Y_n$ is C or T;
$Y_n$ is A, G, C or T if $X_n$ is C, and A or G if $X_n$ is T;
$W_n$ is C or A if $Z_n$ is G or A, and C if $Z_n$ is C or T;
$Z_n$ is A, G, C or T if $W_n$ is C, and A or G if $W_n$ is A;
$QR_n$ is TC if $S_n$ is A, G, C or T, and AG if $S_n$ is T or C;
$S_n$ is A, G, C or T if $QR_n$ is TC, and T or C if $QR_n$ is AG; and, subscript numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

5. A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin consisting essentially of a plus strand having the sequence:

5'-TTK$_{1}$GTL$_{2}$AAK$_{3}$CAJ$_{4}$CAK$_{5}$X$_{6}$TY$_{6}$TGK$_{7}$GG-L$_{8}$QR$_{9}$S$_{9}$CAK$_{10}$X$_{11}$TY$_{11}$GTL$_{12}$GAJ$_{13}$GCL$_{14}$X$_{15}$-TY$_{15}$TAK$_{16}$X$_{17}$TY$_{17}$GTL$_{13}$TGK$_{19}$GCL$_{20}$GAJ$_{21}$-W$_{22}$GZ$_{22}$GCL$_{23}$TTK$_{24}$TTK$_{25}$TAK$_{26}$ACL$_{27}$CC-L$_{28}$AAJ$_{29}$ACL$_{30}$W$_{31}$GZ$_{31}$W$_{32}$GZ$_{32}$GAJ$_{33}$GCL$_{3-4}$GAJ$_{35}$GAK$_{36}$X$_{37}$TY$_{37}$CAJ$_{38}$GTL$_{39}$GGL$_{40}$CAJ-$_{41}$GTL$_{42}$GAJ$_{43}$X$_{44}$TY$_{44}$GGL$_{45}$GGL$_{46}$GGL$_{47}$CC-L$_{48}$GGL$_{49}$GCL$_{50}$GGL$_{51}$QR$_{52}$S$_{52}$X$_{53}$TY$_{53}$CAJ$_{54}$-CCL$_{55}$X$_{56}$TY$_{56}$GCL$_{57}$X$_{58}$TY$_{58}$GAJ$_{59}$GGL$_{60}$Q-R$_{61}$S$_{61}$X$_{62}$TY$_{62}$CAJ$_{63}$AAJ$_{64}$W$_{65}$GZ$_{65}$GGL$_{66}$AT-M$_{67}$GTL$_{68}$GAJ$_{69}$CAJ$_{70}$TGK$_{71}$TGK$_{72}$ACL$_{73}$-QR$_{74}$S$_{74}$ATM$_{75}$TGK$_{76}$QR$_{77}$S$_{77}$X$_{78}$TY$_{78}$TAK$_{79}$-$_{9}$CAJ$_{80}$X$_{81}$TY$_{31}$GAJ$_{32}$AAK$_{83}$TAK$_{34}$TGK-$_{85}$AAK$_{86}$TAG-3' wherein

A is deoxyadenyl,
G is deoxyguanyl,
C is deoxycytosyl,
T is thymidyl,
J is A or G;
K is T or C;
L is A, T, C, or G;
M is A, C or T;
$X_n$ is T or C if $Y_n$ is A or G; and C if $Y_n$ is C or T;
$Y_n$ is A, G, C or T if $X_n$ is C, and A or G if $X_n$ is T;
$W_n$ is C or A if $Z_n$ is G or A, and C if $Z_n$ is C or T;
$Z_n$ is A, G, C or T if $W_n$ is C, and A or G if $W_n$ is A;
$QR_n$ is TC if $S_n$ is A, G, C or T, and AG if $S_n$ is T or C;
$S_n$ is A, G, C or T if $QR_n$ is TC, and T or C if $QR_n$ is AG; and, subscript numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

6. A microorganism transformed by the transfer vector of claim 4 or 5.

7. The plasmid pcHI-1.

8. The plasmid pcHP-1.

9. A microorganism transformed by the plasmid of claim 7 or 8.

10. A microorganism as in claim 9 wherein the organism is *Escherichia coli.*

11. The microorganism as in claim 10 wherein the organism is *Escherichia coli* HB-101.

12. The DNA transfer vector of claim 4 wherein:
J is A in amino acid positions 4, 13, 21, 69 and 70;
J is G in amino acid positions 29, 33, 34, 38, 41, 43, 54, 59, 63, 64, 80 and 82;
K is T in amino acid positions 1 and 72;
K is C in amino acid positions −5, 3, 5, 7, 10, 16, 19, 24, 25, 26, 36, 71, 76, 79, 83, 84, 85 and 86;
L is A in amino acid positions −7, −4, −2, 27, 34 and 50;
L is T in amino acid positions −6, 14, 48 and 49;
L is C in amino acid positions −23, −16, −10, −3, −1, 8, 23, 28, 30, 45, 47, 51, 55, 57, 66 and 73;
L is G in amino acid positions −13, 2, 12, 18, 20, 39, 40, 42, 46, 60 and 68;
M is C in amino acid position 75;
M is T in amino acid position 67;
X is T in amino acid position 56;
X is C in amino acid positions −22, −18, −17, −15, −14, −12, −11, −9, 6, 11, 15, 17, 37, 53, 58, 62, 78 and 81;
X is G in amino acid position 44;
Y is A in amino acid position 17;
Y is G in amino acid positions −22, −17, −15, −14, −12, −11, −9, 6, 11, 37, 44, 53, 56, 58, 62 and 81;
Y is C in amino acid positions −18, 15 and 78;
W is C in amino acid positions −19, 22, 31, 32 and 65;
Z is C in amino acid position −19;
Z is A in amino acid position 22;
Z is G in amino acid positions 31 and 32;
Z is T in amino acid position 65;
QR is TC in amino acid positions 9, 62 and 77;
QR is AG in amino acid positions 52 and 74;
S is A in amino acid position 9; and
S is C in amino acid positions 52, 61, 74 and 77.

13. The DNA transfer vector of claim 5 wherein:

J is A in amino acid positions 4, 13, 21, 69 and 70;
J is G in amino acid positions 29, 33, 35, 38, 41, 43, 54, 59, 63, 64, 80 and 82;
K is T in amino acid positions 1 and 72;
K is C in amino acid positions 3, 5, 7, 10, 16, 19, 24, 25, 26, 36, 71, 76, 79, 83, 84, 85 and 86;
L is A in amino acid positions 27, 34 and 50;
L is T in amino acid positions 14, 48 and 49;
L is C in amino acid positions 8, 23, 28, 30, 45, 47, 51, 55, 57, 66 and 73;
L is G in amino acid positions 2, 12, 18, 20, 39, 40, 42, 46, 60 and 68;
M is C in amino acid position 75;
M is T in amino acid position 67;
X is T in amino acid position 56;
X is C in amino acid positions 6, 11, 15, 17, 37, 53, 58, 62, 78 and 81;
X is G in amino acid position 44;
Y is A in amino acid position 17;
Y is G in amino acid positions 6, 11, 37, 44, 53, 56, 58, 62 and 81;
Y is C in amino acid positions 15 and 78;
W is C in amino acid positions 22, 31, 32 and 65;
Z is A in amino acid position 22;
Z is G in amino acid positions 31 and 32;
Z is T in amino acid position 65;
QR is TC in amino acid positions 9, 62 and 77;
QR is AG in amino acid positions 52 and 74;
S is A in amino acid position 9; and
S is C in amino acid positions 52, 61, 74 and 77.

14. The DNA transfer vector of claim 5 wherein the codon for amino acid position one is preceded by 5'-ATG and
J is A in amino acid positions 13, 21, 69 and 70;
J is G in amino acid positions 4, 29, 33, 35, 38, 41, 43, 54, 59, 63, 64, 80 and 82;
K is T in amino acid positions 3, 7 and 72;
K is C in amino acid positions 1, 5, 10, 16, 19, 24, 25, 26, 36, 71, 76, 79, 83, 84, 85 and 86;
L is A in amino acid positions 27, 34, 50;
L is T in amino acid positions 8, 12, 14, 48 and 49;
L is C in amino acid positions 2, 23, 28; 30, 45, 47, 51, 55, 57, 66 and 73;
L is G in amino acid positions 18, 20, 39, 40, 42, 46, 60 and 68;
M is C in amino acid position 75;
M is T in amino acid position 67;
X is T in amino acid position 56;
X is C in amino acid positions 6, 11, 15, 17, 37, 53, 58, 62, 78, and 81;
X is G in amino acid position 44;
Y is A in amino acid position 17;
Y is G in amino acid positions 37, 44, 53, 56, 58, 62, and 81;
Y is C in amino acid positions 11, 15 and 78;
Y is T in amino acid position 6;
W is C in amino acid positions 22, 31, 32 and 65;
Z is A in amino acid position 22;
Z is G in amino acid positions 31 and 32;
Z is T in amino acid position 65;
QR is TC in amino acid positions 9, 62 and 77;
QR is AG in amino acid positions 52 and 74
S is T in amino acid position 9; and
S is C in amino acid positions 52, 61, 74 and 77.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. :4,431,740 

DATED :FEBRUARY 14, 1984

INVENTOR(S) :GRAEME BELL ET AL

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 17:

Claim 4, line 11 of "$GCL_{20}$" should read --$GGL_{20}$--;

Claim 4, line 12, "$CL_{23}$" should read --$GL_{23}$--;

Claim 5, line 6, "$GCL_{20}$" should read $GGL_{20}$--;

Claim 5, line 7, "$GCL_{23}$" should read --$GGL_{23}$--;

Column 15, Claim 12, line 3, "34" should read --35—.
Claim 12, line 31 "QR is TC in amino acid positions 9, 62 and 77; should read --QR is TC in amino acid positions 9, 61 and 77;—

Column 19, Claim 13, line 28 "QR" is TC in amino acid positions 9, 61 and 77;—

Column 20, Claim 14, line 31 "QR is TC in amino acid positions 9, 62 and 77;" should read —QR is TC is amino acid positions 9, 61 and 77;—.

Signed and Sealed this

Twenty-fifth Day of January, 1994

*Attest:*

Bruce Lehman

BRUCE LEHMAN

*Attesting Officer*

*Commissioner of Patents and Trademarks*

# UNITED STATES PATENT AND TRADEMARK OFFICE
# CERTIFICATE OF CORRECTION



PATENT NO. : 4,431,740

DATED : FEBRUARY 14, 1984

INVENTOR(S) : GRAEME BELL ET AL

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 22 "diabetis" should read --diabetes--; line 68, "difficult conventional" should read --difficult using conventional--.

Column 2, line 45 "sequency" should read --sequence--.

Column 3, insert between line 65 and 66 --X = C if Y is C or T--.

Column 4, line 61 "plasmide" should read --plasmid--.

Column 11, line 34 "oligo-dC" should read --oligo-dG--; line 44 and line 63 "ampicillinsensitive" should read --ampicillin sensitive--.

Column 12, line 35 "cDMA" should read --cDNA--.

Column 13, line 16 "these" should read --those--.

Col 1 Table 1, each occurrence "Try" should read --Tyr--.
Col 3 Table 2, "A Adenine" should read --A-Adenine--.
Col 3 Table 3, "Tryptophan(Try)" should read --Tryptophan(Trp)--.

[redacted]